AIDS Rev. 2007;9:173-87

Immunizations in HIV-Infected Adults

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Abstract

The incidence or severity of certain vaccine-preventable diseases is higher in HIV-infected individuals. However, immune responses to vaccination may be diminished, particularly in those with severe immunosuppression. Higher doses of vaccine, more frequent boosters, or revaccination after antiretroviral therapy-induced immune reconstitution are strategies to be considered for patients in certain circumstances. In addition, some vaccines may be harmful when given to severely immunocompromised patients. The challenge for healthcare providers is assessing the safety and effectiveness of vaccines for HIV-infected patients, especially when information on vaccines has not been fully characterized in the HIV-setting. This review presents state-of-the-art knowledge about immunizations for HIV-adults. The efficacy and safety of current vaccines, their current indications in HIV-infected adults, and the strategies aimed to enhance their results are discussed. **(AIDS Rev. 2007;9:173-87)**

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Key words

HIV. Immunization. Vaccines.

Introduction

Immunizations are an excellent opportunity to prevent serious and potentially life-threatening diseases in the care of HIV-infected patients. As HIV may increase the susceptibility of the patient to some preventable diseases, it can also alter the efficacy and safety of vaccinations. The purpose of this article is to review current data about the efficacy and safety of vaccines in HIV-infected individuals and discuss what approaches should be implemented to provide broad and successful immunization to this population. The main recommendations are summarized in tables 1 and 2.

General principles

Immune responses to vaccination vary, depending on the nature of the vaccine and the individual's immune status. In general, humoral and cellular responses to antigens are inversely correlated with the patient's CD4+ T lymphocyte cell count. Malnutrition, concurrent infections and comorbidities in patients with HIV infection may also have a deleterious effect on the immune system and can affect how patients respond to vaccines[1]. Higher doses of vaccine or more frequent boosters may be considered for patients in certain circumstances. Highly active antiretroviral therapy (HAART) can restore the immune response to vaccines and sometimes it may be reasonable to repeat the vaccination or delay the administration of immunizations until after immune reconstitution has occurred.

Regarding safety of vaccination, in general there is no harm in vaccinating HIV-infected patients with inactivated vaccines, although certain live vaccines may be harmful when given to severely immunocompromised patients[1,2].

Another issue is whether vaccines can worsen HIV disease by inducing CD4+ T-cell activation or can lead to increases in HIV-1 replication. Certain vaccines might activate virus replication and transiently decrease CD4+ T-cell count and increase viral load. Whether this event might alter the long-term course of HIV disease is unknown. However, it is likely that effective antiretroviral therapy will control the effects, if any, of vaccination on stimulating HIV replication. In addition, natural infection with a

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Table 1. Practical considerations about main INACTIVATED vaccines in HIV infected adults

	Indication	Safety CD4+ count	Doses for unvaccinated adults	Booster	Comments
Influenza-parenteral vaccine	Routine vaccination	Any	Single dose	Annually	– Beginning in October and continuing through the influenza season – Contraindicated if severe allergy to eggs
23-valent pneumococcal polysaccharide vaccine	Indicated if > 200 cells/mm^3 (consider if < 200 cells/mm^3)	Any	Single dose	Revaccinate once after 5 years or sooner if vaccinated with < 200 cells/µl and increased to > 200 cells/mm^3 while on antiretroviral therapy	– No clinical evidence for efficacy in patients with CD4 < 200 cells/mm^3
Tetanus-diphtheria ± pertussis vaccine	Routine vaccination	Any	3 adult doses at 0, 1, 6-12 months, first dose preferably Tdap	10 years	– Tdap vaccine for next booster (see text) – There is no need to restart a series regardless of the time elapsed between doses
Hepatitis A	Routine vaccination	Any	Two doses 6-12 months apart	Efficacy probably life-long, consider revaccination once the CD4 count has risen > 500 cells/mm^3	– Mainly indicated in travelers, MSM, chronic liver disease, IDU, hemophilia – Adult HAV+HBV combined vaccine should be administered at 0,1, 6 months
Hepatitis B	Routine vaccination	Any	3 doses at 0, 1, and 6 months	Consider one booster when anti-HBs concentrations decline to < 10 mIU/ml	– Consider three further single or double doses one month apart for HBV vaccine nonresponders
Haemophilus influenzae	Patients at risk	Any	Single dose	Consider one booster after treatment-induced immune reconstitution	– Indicated if acquire splenic dysfunction, recurrent pulmonary infections or contacts of a case of invasive disease
Meningococcus C or quadrivalent meningococcal vaccine (ACYW-135)	Young adults (< 18-25 years of age) and patients at risk	Any	Single dose	No boosting is recommended for conjugated vaccines. One single dose every 3 years for polysaccharide vaccines if risks persist	– Mainly indicated if functional or anatomic asplenia, complement deficiencies, travel exposure, college students living in dormitories, or military recruits
Inactivated polio vaccine	All unvaccinated adults	Any	3 doses at 0, 1-2, 6-12 months	One single dose after 10 years if at risk	– Risk in travelers to South Asia and Africa
Quadrivalent papillomavirus vaccine	Females aged 11-26 years	Any	3 doses at 0, 2, 6 months	Not determined	– Full benefit for females not yet sexually active

Tdap: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; MSM: men who have sex with men; IDU: intravenous drug-users. These recommendations may differ slightly according to national guidelines.

Table 2. Practical considerations about main LIVE vaccines in HIV infected adults

	Indication	Safety CD4+ count	Doses for unvaccinated adults	Booster	Comments
Measles, mumps, and rubella (MMR) vaccine	Measles, mumps or rubella seronegative	> 200 cells/mm^3	Two doses, at least one month apart	Protection probably life-long	– Prior serological testing may be used to determine immunity – Mainly indicated in measles-seronegative individuals and rubella-seronegative HIV-infected women of child-bearing age – Pregnancy should be avoided for 1 month after vaccination
Varicella-zoster virus (chickenpox)	Varicella seronegative	> 200-400 cells/mm^3	Two doses, at least 6-8 weeks apart	Duration of protection uncertain (probably > 10 years)	– Prior serological testing may be used to determine immunity – Pregnancy should be avoided for 1 month after vaccination
Zoster vaccine (shingles)	Contraindicated				– Varicella-zoster virus titer at least 5-times greater than that in the chickenpox vaccine
Yellow fever vaccine	Travelers to endemic areas	> 200 cells/mm^3	Single dose	10 years	– Endemic in various tropical areas in Africa and South America – The certificate of vaccination is valid 10 years – Contraindicated if allergy to eggs – Pregnancy should be avoided for 1 month after vaccination
Tuberculosis (BCG)	Contraindicated				
Live intranasal influenza vaccine	Contraindicated				– Use Influenza-parenteral vaccine instead
Smallpox vaccine	Contraindicated				– Very rare exceptions such as personnel working with orthopox viruses
Live oral typhoid vaccine	Contraindicated				– Use inactivated parenteral typhoid vaccine instead
Live oral polio vaccine	Contraindicated				– Use inactivated parenteral polio vaccine instead

BCG: bacilli Calmette-Guérin. These recommendations may differ slightly according to national guidelines.

pathogen for which vaccination provides protection may result in greater stimulation of HIV replication than that produced by vaccination. In the clinical setting it is important for the clinician to avoid checking patients' viral load for several weeks after the administration of immunizations, or at least take into account that a transient viral load elevation may be not related to a treatment failure. Available evidence indicates that these transient increases do not have clinical significance and should not preclude the use of any vaccine.

Inactivated vaccines

Influenza

Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with HIV infection. Several reports indicate that, together with a higher susceptibility to infection, influenza symptoms might be prolonged and the risk for complications and

mortality from influenza is increased for certain HIV-infected persons[3-5]. Current evidence suggests that influenza vaccines are effective, albeit moderately, in reducing the incidence of influenza in HIV-infected individuals. A randomized controlled trial in 102 HIV-infected patients (mean CD4+ T-cell count 400/mm^3, with 13% having values < 200/mm^3) showed that vaccination was associated with significant reductions in respiratory symptoms (29 vs. 49%) and laboratory-confirmed symptomatic influenza (0 vs. 21%)[6]. A recent meta-analysis of four studies revealed vaccine effectiveness ranged from 27 to 78% and that between three and seven people would need to be vaccinated to prevent one case of influenza[7]. Among persons who have advanced HIV disease and low CD4+ T-cell counts, inactivated influenza vaccine might not induce protective antibody titters, even after a booster vaccination with the same vaccine administered one month later or a double dose of the same vaccine[8]. During treatment with HAART, reconstitution of the immune response against influenza antigens occurs[9].

Influenza vaccination might cause a small transient increase in HIV replication, but deterioration of CD4+ T-cell count or progression of HIV disease has not been demonstrated among HIV-infected persons after influenza vaccination compared with unvaccinated persons[6,8,10].

Current guidelines recommend that all HIV-infected patients receive inactivated influenza vaccine annually regardless of their immunologic status[2,5,11]. The intranasal live attenuated influenza vaccine is not currently recommended for HIV-infected persons.

Despite current recommendations, influenza vaccination coverage in HIV-infected individuals is reported to be low. In the USA, despite increases in vaccine coverage in recent years, vaccination only reached around 40% of the HIV-infected population in the 2002 influenza season[12]. Therefore, more efforts should be undertaken to increase influenza vaccination in this population.

Pneumococcal vaccine

The pneumococcus continues to cause significant morbidity and mortality among HIV-infected individuals[13]. The incidence of invasive pneumococcal disease apparently remains high, even after the introduction of HAART[14], although other authors reported a decrease in this incidence since the advent of HAART in the developed world[15]. Major risk factors for invasive pneumococcal disease in the HAART era are similar to those reported in HIV-negative individuals and include associated comorbidity, alcoholism, prior hospitalization, CD4+ T-cell < 100 cells/mm^3 and current smoking[15].

Two different pneumococcal vaccines have been developed: the pneumococcal polysaccharide vaccine, composed of purified preparations from 23 different serotypes (PPV-23), and the 7-valent conjugate pneumococcal vaccine. Currently, there are insufficient data to suggest any advantage of using the conjugate pneumococcal vaccine over the standard polysaccharide vaccine in HIV-infected adults[16].

More than 80% of healthy young adults who receive PPV-23 develop antibodies against the serotypes contained in the vaccine, usually within two to three weeks after vaccination[17]. The HIV-infected persons may have a diminished antibody response to pneumococcal vaccine and this reduction corresponds to the degree of immunodeficiency. Responses are often lower in HIV-infected patients with CD4+ T-cell counts < 500 cells/mm^3 than in those with higher CD4 counts[18]. Among HIV-infected low-level responders, revaccination with a double dose of pneumococcal vaccine does not stimulate responses[19]. In HIV-infected patients under HAART with > 200 CD4+ T-cell/mm^3 (even patients with prior severe immunological impairment), the immunogenicity conferred by the polysaccharide vaccine might be at least as good as that observed in healthy subjects[20]. Conversely, studies on the clinical efficacy of pneumococcus vaccination in HIV-infected adults have reported inconsistent findings. Case-control studies among HIV-infected people in developed countries who have access to antiretrovirals have generally shown protection from invasive disease among those who have received the 23-valent pneumococcal vaccine[13]. One large, prospective, multicentre observational study in the USA demonstrated a reduced incidence of pneumococcal disease in vaccine recipients with CD4+ T-cell counts > 500 cells/mm^3, but not in those with lower CD4+ T-cell counts[21]. Nevertheless, one randomized trial of this vaccine among HIV-infected Ugandan adults without access to antiretrovirals showed an increase in pneumonia among vaccine recipients, and a six-year follow-up of that study showed no further increase in pneumonia, but a paradoxical significant 16% reduction in mortality in the vaccinated group[22].

As a conclusion, the vaccine is likely to be less effective in drug-naive patients with CD4+ T-cell count < 200 cells/mm^3 (those who are at the greatest risk of pneumococcal disease). American guidelines recommend vaccination for adults and adolescents who have a CD4+ T-cell count of > 200 cells/mm^3 with a single dose of PPV-23 if they have not received this vaccine during the previous five years, and indicate that vaccination should also be considered for patients with CD4+ T-cell <200 cells/mm^3, although there is no clinical evidence for efficacy[2]. Similar recommendations are given in more recent British guidelines from the British HIV Association[11]. In persons who received the vaccine when their CD4+ T-cell count is < 200 cells/mm^3, revaccination

should be considered following CD4+ T-cell count increase > 200 cells/mm^3 induced by HAART[2,11].

Diphtheria, tetanus, and pertussis vaccines

Immunity against tetanus in HIV-infected patients tends to be similar to that of the age-matched normal population. Adults who received full primary vaccination before acquiring HIV infection may have sufficient humoral immunity several years after previous vaccination and are likely to develop protective levels of antitoxin following vaccination, even though booster-dose responses are generally inversely correlated to the CD4+ T-cell count[23,24]. Recovery from tetanus may not result in immunity, and vaccination following tetanus is indicated[25]. Regarding the immunity to diphtheria, as with tetanus, adults who receive full primary vaccinations before acquiring HIV infection have been shown to have levels of antibody similar to noninfected controls; however the response to a booster of diphtheria toxoid is significantly reduced[24]. Limited data is available about the antibody response to pertussis vaccine in HIV-infected persons.

Preparations of diphtheria, tetanus, and pertussis vaccinations include diphtheria toxoid (at varying doses), tetanus toxoid, and either whole cell or acellular pertussis vaccine. Whole cell pertussis-containing vaccines are no longer recommended in western countries because this vaccine causes more adverse reactions than acellular pertussis vaccine. Current guidelines recommend updating tetanus and diphtheria immunizations in HIV-infected individuals according to routine recommendations for adults. Classically, a booster dose of tetanus toxoid and the reduced diphtheria toxoid in the form of tetanus-diphtheria (Td) is recommended at 11-12 years of age and at 10-year intervals throughout life[2]. However, recent U.S. guidelines for adults aged 19-64 years, including those with HIV infection, have recently been changed to recommend substituting the new tetanus, diphtheria, acellular pertussis (Tdap) vaccine for the standard Td vaccine with the next booster dose. The rationale for using Tdap instead of Td is to provide additional protection against pertussis[26]. Only a single dose of Tdap is recommended. The duration of protection is not known, nor is the need for subsequent booster doses of acellular pertussis vaccine. Subsequent tetanus doses in the form of Td should be given at 10-year intervals throughout adulthood. For adults who require tetanus toxoid-containing vaccine as part of wound management, a single dose of Tdap is preferred to Td if they have not previously received Tdap. Further research is needed to establish the safety and immunogenicity of Tdap among adults aged ≥ 65 years[26]. Two booster Tdap vaccines have been approved by the Food and Drug Administration (FDA): Boostrix® approved for use in children and adolescents 10-18 years of age and Adacel® approved for use in individuals 11-64 years of age[27].

Hepatitis A and HIV interactions

The prevalence of hepatitis A virus (HAV) antibodies in subjects infected or at risk for HIV, such as intravenous drug users (IDU), men who have sex with men (MSM) and persons frequently exposed to blood products is very high[28,29]. Outbreaks of acute hepatitis A among HIV groups, such as IDU, have been associated with high fatality rates[30]. In addition, HAV superinfection is associated with a high risk of liver failure and death in patients with underlying chronic hepatic illnesses, which are frequent in HIV-infected patients, either as result of hepatitis C, alcohol, steatohepatitis, etc.[31]. Outbreaks of acute hepatitis A in these groups support the need for developing programs of routine vaccination in these populations[30,32].

Mean time to normalization of serum alanine (ALT) and aspartate (AST) aminotransferases seems to be longer in HIV-infected patients compared to healthy controls following episodes of acute hepatitis A[33]. Moreover, HAV viral load is higher and the duration of HAV viremia longer in HIV-infected patients than in healthy individuals[34]. A median duration of 53 days of HAV viremia was found in a study conducted in HIV-infected MSM, significantly longer than in uninfected persons suffering from acute hepatitis A (median, 22 days). This longer period of HAV viremia, and therefore infectivity, might explain the characteristic long-lasting outbreaks of HAV infection among HIV-infected communities of MSM[34]. At this time is unclear whether higher peaks of viremia and prolonged duration in the HIV setting may be associated with more severe liver damage, including fulminant hepatitis.

On the other hand, acute hepatitis A may trigger HIV replication[35], although this is not universal and some studies have not shown significant changes in CD4+ T-cell counts and/or in HIV viremia within the six months following the onset of acute symptoms[33,34]. Moreover, the morbidity of acute hepatitis A does not seem to be increased in HIV-infected persons, at least not among severely immunocompromised patients, although data in this subset of patients is rather scarce[33,34,36]. Finally, concerns about the use of antiretroviral drugs during episodes of acute hepatitis A have prompted to interrupt therapy; there is no evidence for a detrimental effect of HAART on the course of hepatitis A and therefore antiretroviral medications should not be discontinued[37].

Hepatitis A vaccines

Inactivated and attenuated hepatitis A vaccines have been developed and evaluated in human clinical trials

and in nonhuman primate models of HAV infection. However, only vaccines made from inactivated HAV have been evaluated for efficacy in controlled clinical trials[38]. Vaccines containing HAV antigens that are currently licensed in the USA are the single-antigen vaccines Havrix® and Vaqta® and the combined vaccine Twinrix®, which contains both HAV and HBV antigens. Aventis Pasteur (Lyon, France) has licensed a hepatitis A vaccine called Avaxim® in Europe, Canada, and other countries. Another HAV vaccine named Epaxal® has been developed at the Swiss Serum Institute and is in most European countries, South America, Canada and other parts of the world. All are inactivated hepatitis A vaccines and are produced in similar ways, with only different manufacturing processes.

Hepatitis A vaccines are safe, highly and rapidly immunogenic, and provide durable protection against HAV infection in healthy persons who receive the recommended doses. Within one month of receiving the first dose, 97% of children and adolescents and 95% of adults develop protective levels of HAV antibody. Within one month of receiving the second dose, virtually all recipients achieve protective levels of HAV antibody. All hepatitis A vaccines are highly efficacious in protecting against symptomatic acute hepatitis A[39].

Adults infected with HIV are less likely to develop a protective antibody response following HAV vaccination, and overall show lower antibody titres than do HIV-uninfected persons. Response rates in this population have ranged from 50 to 94% (Table 3)[40-50]. A recent meta-analysis of eight studies, in which a total of 458 patients were examined, estimated that HAV protection was achieved by only 64% (95% CI: 52-75%) in HIV-infected individuals, using an intent-to-treat analysis[51]. Of note, the overall estimated response rates did not change, regardless of exposure to HAART. In contrast, most studies which have examined the impact of CD4+ T-cell counts on HAV vaccination responses have concluded that lower CD4+ T-cell counts are associated with a diminished HAV vaccine response. In one study conducted between 1995 and 1997, Kemper, et al. found that patients with CD4+ T-cell count < 200 cells/mm^3 had significantly lower response rates to HAV vaccine than those with higher CD4+ T-cell counts (9 vs. 68%)[46]. In a more recent trial, Wallace, et al. examined 49 HIV-infected subjects, 76% of whom were on protease inhibitors, and found that all with a CD4+ T-cell count > 300 cells/mm^3 seroconverted, while only 87% of those with a CD4+ T-cell count < 300 cells/mm^3 seroconverted[44]. Finally, Weissman, et al. reported that female gender and CD4+ T-cell counts at vaccination, but not the CD4+ T-cell nadir, predicted response to HAV vaccine[47]. In a retrospective study, Overton, et al. reported in a conference that only the suppression of viral replication (plasma HIV-RNA < 1000 copies/ml) at the time of vaccination was independently associated with response to HAV vaccination[48]. In the article published later, male gender was included as a factor associated with a protective antibody response[52]. These authors did not find any independent association with the CD4+ T-cell nadir nor with the CD4+ T-cell count at the time of vaccination.

On the basis of all these data, some experts feel that patients receiving antiretroviral therapy should wait to receive hepatitis A vaccine until immunologic reconstitution has been achieved[47,49]. In contrast, others consider that serologic responses are good enough even among subjects with CD4+ T-cell counts < 300/mm^3 and, therefore, they favor that HAV vaccine should be provided to all HIV-positive individuals lacking HAV antibody[37].

The HAV vaccine is safe in HIV-infected patients, with rates of adverse events comparable to those in HIV-negative patients[49,51]. All studies conducted in the HAART era have failed to detect any significant deleterious effect of vaccination on HIV disease, with no demonstrable effect on plasma viremia, progression to AIDS, or CD4+ T-cell count decline. Overall, the expected rise in viral load following any vaccination is blunted when antiretroviral therapy is used[44].

Our recommendation for clinical practice is that the vaccine should be provided to all non-immunized HIV-positive individuals on a standard basis. Nonresponders to the HAV vaccine should be revaccinated once their CD4+ T-cell count has risen, ideally above 500 cells/mm^3, in response to HAART[37,53].

Hepatitis B and HIV interactions

Exposure to hepatitis B virus (HBV) is very common in persons at risk from having HIV infection, and the prevalence of chronic hepatitis B is not surprisingly among the highest in this population. In Western Europe and the USA, the prevalence of chronic HBV infection ranges from 4 to 14%, being 9-17% among MSM, 7-10% among IDU, and 4-6% among persons infected through heterosexual contact[54-57]. The natural history of hepatitis B disease is deleteriously influenced by HIV, with an accelerated progression to hepatic cirrhosis and end-stage liver disease. Increased HBV carriage rates, greater levels of HBV plasma viremia, more rapid decline in antibody titres to the hepatitis B surface antigen (anti-HBs) and reactivation of latent hepatitis B, are all situations characteristically reported in HBV/HIV-coinfected populations[58]. Moreover, hepatocellular carcinoma may develop at a younger age and is more aggressive in this subset of patients[59].

In the Multicentre AIDS Cohort Study (MACS) cohort, an increased risk of liver-related mortality was seen among HBV/HIV-coinfected compared to HIV-monoin-

Table 3. Immunogenicity of hepatitis A vaccines in HIV-infected adults

Study (year)	$CD4^+$ count at time of vaccine ($cells/mm^3$)	Age (years)	Vaccine and dose	No. of HIV subjects completing the study	Response rates
Santagostino, et al. (1994)[40]	32% < 200	Median 21 (pediatric population included)	HAVRIX (720 EIU at 0, 1, and 6 months)	47	77%
Hess, et al. (1995)[41]	495 (mean)	Mean 33.2	HAVRIX (720 EIU at 0, 1, and 6 months)	14	79%
Tilzey, et al. (1996)[42]	Not reported	Median 31	HAVRIX (720 EIU at months 0, 1, and 6; four subjects received 1440 EIU booster)	17	76.5%
Neilsen, et al. (1997)[43]	515 (mean)	Mean 33.3	HAVRIX (1440 EIU, either 1 or 6 months apart)	76	88%
Wallace, et al. (1999)[44]	50% < 300	Mean 32.6	VAQTA (weeks 0 and 24)	49	94%; (100% in patients with > 300 CD4)
Valdez, et al. (2000)[45]	372 (median)	Median 39	HAVRIX (1440 IU/0.5ml at baseline and week 6)	15	73%
Kemper, et al. (2003)[46]	376 (mean)	Mean 38	HAVRIX (1440 EIU, 6 months apart)	39	51%
Weissman, et al. (2004)[47]	424 (mean)	Mean 43	HAVRIX (1440 EIU 6-12 months apart)	138	48.5%
Overton, et al. (2005)[48]	438 (median)	Mean 40.5	At least 1 dose of HAVRIX, 1440 EIU	235	48%
Rimland, et al. (2005)[49]	Not reported	Not reported	Two doses of HAVRIX	214	61%
Loutan, et al. (2007)[50]	557 (mean)	Mean 34.8	Two doses of EPAXAL 12 months apart	13	91.7%

EIU: ELISA units.

fected individuals, particularly among coinfected patients with low CD4+ T-cell nadir counts[56]. The effect of HBsAg positivity on progression to AIDS, death from all causes, liver disease-related death and response to HAART was further examined in the EuroSIDA cohort. Among 5728 HIV-positive individuals tested for HBsAg, 498 (8.7%) were positive. This large study confirmed a threefold higher increased risk of liver disease among HBsAg-positive patients compared to a control group of HBsAg-negative HIV-infected individuals. Deaths related to AIDS occurred at similar rates in both groups of patients. Moreover, immunologic and virologic responses following HAART initiation did not differ significantly[57]. Interestingly, CD4+ T-cell count gains with HAART reduced significantly the risk of death from liver disease in the HBV/HIV-coinfected population, supporting that HAART is particularly useful in this population.

Hepatitis B vaccines

Safe and effective hepatitis B vaccines have been commercially available since 1982. The first available vaccines were produced by harvesting HBsAg from the plasma of people with chronic HBV infection. Subsequently, several vaccine manufacturers used recombinant DNA technology to express HBsAg in other organisms, which led to the development of recombinant DNA vaccines. Plasma-derived vaccines are no longer produced by manufacturers in North America or Western Europe, but are still produced by some manufacturers in Asia, and are used in many immunization programs worldwide. Hepatitis B vaccine is available as a single-antigen formulation and also in fixed combinations with other vaccines.

Two single-antigen vaccines are available in the United States: Recombivax HB® and Engerix-B®. Of

the three licensed combination vaccines, one (Twinrix®) is used for vaccination of adults and two (Comvax® and Pediarix®) are used for vaccination of infants and young children. Twinrix® contains recombinant HBsAg and inactivated HAV, while Comvax® and Pediarix® contain several other antigens[60,61].

No significant, distinctive, adverse clinical reactions to HBV vaccination have been described in the HIV-infected population. Transient elevations in plasma HIV-RNA lasting for several days or a few weeks have been sporadically reported following HBV immunization. None of these investigations has demonstrated prolonged viral load rises, CD4+ T-cell count declines, or accelerated HIV disease progression following HBV immunization[37].

Primary HBV vaccination consists of three or more intramuscular doses of the hepatitis B vaccine. The three-dose vaccine series administered intramuscularly at 0, 1, and 6 months produces a protective antibody response in approximately 30-55% of healthy adults aged < 40 years after the first dose, 75% after the second dose, and > 90% after the third dose. Only less than 10% of healthy immunocompetent subjects do not mount an appropriate HBV antibody response (anti-HBs). Nonresponse is defined as an anti-HB level < 10 mIU/ml measured 1-6 months after the last dose of a full immunization. After the age of 40 years, the proportion of persons who mount a protective antibody response after a three-dose HBV vaccination regimen declines to < 90%, and by age 60 years, protective levels of HBV antibody are elicited in only 75% of vaccinated persons[60]. Besides age, nonresponse is influenced by different HLA-DR alleles, impaired Th cell responses, the route of injection, gender, body mass, and other unidentified factors[61].

The immunogenicity of hepatitis B vaccines is impaired in patients with HIV infection. In fact, lack of response to hepatitis B vaccines is much more common than for hepatitis A vaccines because HBV immunogenicity is much more sensitive to CD4+ T-cell counts[37]. Studies conducted among HIV-positive patients during the late 1980s and 1990s demonstrated response rates of 17-56% using both recombinant and plasma-derived hepatitis B vaccines, and the response was greatly influenced by the CD4+ T-cell count[62-73] (Table 4). In HIV-positive patients experiencing good responses, protective antibody titers were noted to be lower than in HIV-negative counterparts. Furthermore, after achieving an adequate HBV antibody response following vaccination, HIV-infected individuals are less likely to maintain sustained high and protective anti-HBs titers[74].

Immunocompetent persons who achieve anti-HBs concentrations > 10 mIU/ml after vaccination have nearly complete protection against HBV infection[60]. After primary immunization with the hepatitis B vaccine, anti-HBs levels generally decline rapidly within the first year and more slowly thereafter. Among young adults who respond to a primary HBV vaccine series with antibody concentrations > 10 mIU/ml, 17-50% have low or undetectable concentrations of anti-HBs (reflecting anti-HBs loss) 10-15 years after HBV vaccination. This phenomenon is deemed “waning antibody” or “waning immunity,” as opposed to true nonresponse. Even when anti-HBs concentrations decline to < 10 mIU/ml, nearly all immunocompetent vaccinated persons remain protected against HBV infection[60]. The mechanism for continued vaccine-induced protection is thought to be the preservation of immune memory by selective expansion and differentiation of clones of antigen-specific B and T lymphocytes immediately after HBV exposure.

Although immunogenicity is lower among immunocompromised persons, those who achieve and maintain a protective HBV antibody response show high levels of protection against HBV infection. No clinically significant HBV infections have been documented among immunocompromised persons who maintain protective levels of anti-HBs. Limited data are available on the duration of immune memory after hepatitis B vaccination in HIV-infected patients. In studies conducted in HIV-infected persons under long-term follow-up, breakthrough infections occurred only when a decline in anti-HBs concentrations to < 10 mIU/ml had occurred. In most cases, these acute hepatitis B episodes were transient and asymptomatic. Conversely, in other immunocompromised individuals such as hemodialysis patients who previously had responded to the HBV vaccine, clinical episodes of acute hepatitis B have been reported in persons who have not maintained anti-HBs concentrations > 10 mIU/ml[60].

It is difficult to distinguish between waning immunity and nonresponse in individuals with an unknown anti-HBs response following HBV immunization. A single dose of vaccine, however, may be helpful in this regard. The degree of anti-HBs response 4-12 weeks after a single booster dose may differentiate the two antibody response patterns. True nonresponders will have no elicit serum anti-HBs level or a very small rise, whereas those with waning HBV antibody generally will have a robust response, usually > 10 mIU/ml[75].

Clinical algorithms to re-immunize nonresponders have been investigated in HIV-infected persons who have not experience adequate responses to the initial HBV vaccination. Among other schedules, doubling the standard antigen dose or administering additional doses has been investigated in order to improve the response rates[75]. In HIV-infected patients, this may be attempted in any of three ways – increasing the number and size of vaccine doses, using immune stimulants/vaccine adjuvants, and raising the CD4+ T-cell

Table 4. Immunogenicity of hepatitis B vaccines in HIV-infected adults

Study	Year	Vaccine	No. of subjects completing the study	Response rates
Collier, et al.[62]	1988	Plasma- derived	16	56%; titers lower than in controls
Keet, et al.[63]	1992	Recombinant	32	28%; titers lower than in controls
Bruguera, et al.[64]	1992	Recombinant	21	24%; response only in patients with CD4 count > 700 cells/mm^3
Tayal, et al.[65]	1994	Recombinant	12	17%; poor response to additional dose
Wong, et al.[66]	1996	Plasma-derived or recombinant	14	43%
Rey, et al.[67]	2000	Recombinant	20	55% after 3 injections; 78% of 9 nonresponders after 3 additional doses
Ahuja, et al.[68]	2005	Recombinant	116	53%;HIV+ adults receiving hemodialysis
Pasricha, et al.[69]	2005	Recombinant	40	100% if CD4 counts > 200 cells/mm^3; 47% if CD4 counts < 200 cells/mm^3
Overton, et al.[70]	2005	Recombinant	194	17.5%; response associated to plasma HIV-RNA < 400 copies/ml
Fonseca, et al.[71]	2005	Recombinant (2 different doses)	210	34% with 20 µg and 47% with 40 µg ($p = 0.07$)
Cornejo-Juarez, et al.[72]	2006	Recombinant (2 different doses)	79	61.5% with 10 µg and 60% with 40 µg; response associated to CD4 counts > 200 cells/mm^3
Veiga, et al.[73]	2006	Recombinant	55	59% better response if CD4 counts > 450 cells/mm^3 and undetectable plasma HIV-RNA

count. However, limited data exist regarding the response to these alternative vaccination schedules.

In the absence of HAART, a single additional dose of hepatitis B vaccine generally has no beneficial impact on seroconversion[63]. One small study showed that doubling the number of doses of the GenHevac B® vaccine (Sanofi-Pasteur, Lyon, France), which is not licensed in the USA, and includes the preS2 region of HBV, might significantly improve anti-HBs response rates[67]. In this study, HIV-infected patients with CD4+ T-cell counts > 200 cells/mm^3 and on stable antiretroviral treatment, were given three intramuscular injections of GenHevac B® 20 µg at one-month intervals. Initial nonresponders were given three additional monthly injections. The overall response rate after three 20 µg injections was 55% (11/20). Among nine initial nonresponders, only two did not respond with the three additional doses. Thus, the overall response rate was 90% (18/20).

Another recent study has suggested that doubling the HBV vaccine dose may improve responses in HIV-infected patients, at least in those with higher CD4+ T-cell counts[71]. Among 210 HBV patients with no markers of prior HBV exposure, administration of three doses (at 0, 1, and 6 months) of the Energix-B® vaccine resulted in seroconversion in 34% of patients receiving the standard 20 µg dose versus 47% in those receiving a 40 µg dose ($p = 0.07$). This improvement was confined to patients with CD4+ T-cell counts > 350 cells/mm^3; seroconversion occurred in 64% of this subset of patients using the 40 µg dose but only in 39% of those that used the standard dose. In contrast, in patients with CD4+ T-cells < 350 cells/mm^3, rates of 24% using the 40 µg dose and 26% using the standard dose were seen[71]. In contrast with these results, a recent study, in which two different doses of the HBV Recombivax® vaccine (10 or 40 µg) were used in 79 HIV-infected individuals, failed to demonstrate any significant benefit in the rate of response in 79 HIV-infected patients[72].

Several attempts have been made to increase HBV vaccine responses in HIV nonresponders using vaccine adjuvants. Granulocyte macrophage colony stimulating factor (GM-CSF) has shown to be occasionally

effective while the use of interleukin-2 (IL-2) has not[54]. Other newer adjuvants that may significantly enhance the immunogenicity of the hepatitis B vaccine are currently being tested in HIV-infected patients[37,76].

In conclusion, in patients nonresponding to a standard course of HBV vaccination, higher hepatitis B vaccine doses, prolongation of the vaccination schedule with more doses, or both strategies, may be considered. Ideally, truly HBV vaccine nonresponders should receive up to three further double doses.

Patients with isolated hepatitis B core antibody

Patients positive for antibody to hepatitis B core (anti-HBc) but negative for both HBsAg and anti-HBs testing are infrequently seen in the general population, but more frequently in HIV-infected individuals and/or those with chronic hepatitis C[74]. The significance and implications of isolated anti-HBc is unclear. In subjects with chronic hepatitis C, isolated anti-HBc may reflect the inhibitory interference between HBV and hepatitis C virus (HCV), with a suppression of the former. Low titers of HBsAg along with detectable serum HBV-DNA are occasionally seen in these patients. In immunosuppressed patients, isolated anti-HBc more often reflects clearance of HBsAg, but inability to mount an adequate anti-HBs response or to maintain it over time. Occasionally, an isolated anti-HBc may just result from false-positive results, especially in low-risk populations[61].

At this time it remains uncertain whether individuals who test positive for isolated anti-HBc should be vaccinated against HBV. All subjects showing isolated anti-HBc should be retested. To distinguish the three possibilities previously mentioned (low-level HBV infection, prior immunity with undetectable anti-HBs, or false-positive results), patients may receive a single dose of the hepatitis B vaccine. If anti-HBs become positive at one month with high titers, an anamnestic response should be suspected and no further vaccine injections are necessary. On the other hand, if anti-HBs remains negative after the single HBV vaccine dose, serum HBV-DNA should be tested using a sensitive technique. If low-level HBV-DNA is recognized, the patient should be considered as infected by HBV and therefore does not need any HBV vaccine prophylaxis. In contrast, a negative serum HBV-DNA along with undetectable anti-HBs would suggest that the patient is not infected by HBV nor has been previously exposed and the three-shot vaccine series should be completed.

One study that assessed whether HIV-infected patients with isolated anti-HBc could exhibit an anamnestic response following HBV vaccine concluded that this was the case only for a minority of patients[74]. In fact, anti-HBs appeared at a rate comparable to that seen in subjects who tested negative for anti-HBc. Therefore, the presence of isolated anti-HBc in HIV-infected patients should not be interpreted as a surrogate marker of protection against HBV. Accordingly, these patients should be vaccinated.

Other inactivated vaccines

Haemophilus influenzae *vaccine*

Haemophilus influenzae serotype b (Hib) vaccination is part of the routine childhood vaccination program, but Hib vaccination is not routinely recommended in HIV-positive adults. Adults with advanced HIV disease do have a significantly increased rate of infection with *H. influenzae*, but most infections involve non-typeable strains for which the vaccine is not protective[77,78]. Nevertheless, licensed conjugated Hib vaccines are immunogenic in patients with HIV infection, and baseline CD4+ T-cell count predicts the likelihood of antibody response to vaccine[79]. One single dose may be recommended in several situations such as HIV-infected patients with acquire splenic dysfunction, recurrent pulmonary infections, or those who are contacts of a case of invasive disease[11]. Re-immunization should be considered after HAART-induced immune reconstitution.

Meningococcal vaccine

Among the 13 distinct *Neisseria meningitidis* serogroups that have been defined, groups A, B, C, W-135 and Y are responsible for over 90% of severe meningitis and septicemia. The disease mainly affects children and young adults. Epidemic meningococcal meningitis is an important public health problem in sub-Saharan Africa. Group A meningococci are the major cause of both epidemic and endemic meningococcal disease in Africa, with the highest burden of disease occurring in a sub-Saharan area from Senegal to Ethiopia that is referred to as “the meningitis belt”. Serogroup B meningococcus is the most important cause of endemic meningitis in industrialized countries, accounting for 30-40% of cases in North America and for up to 80% in certain European countries, with most of the remaining cases being caused by group C strains. Group B meningococcus also can cause severe, persistent epidemics such as those which occurred in Latin American countries[80]. Polysaccharide vaccines and newer conjugate vaccines against groups A, C, Y and W-135 meningococci are available. The main difference is that conjugate vaccines induce long-term immune memory[81]. A number of candidate vaccines for group B meningococcal disease are currently under study.

Patients with HIV are likely at increased risk for meningococcal disease[81]. There has been very little data published on either the safety or efficacy of these vaccines in HIV-infected adults, generally showing better responses in those with less advanced disease and no major adverse reactions[11].

Meningococcus vaccination with the conjugate group C vaccine or the newer quadrivalent conjugate vaccines (ACWY) is now part of routine childhood schedules in several developed countries. Young adults (< 18-25 years of age depending on the country) who have not previously been vaccinated are also recommended to receive the vaccine, including HIV-infected individuals[82]. Routine vaccination also is recommended for certain persons who have increased risk for meningococcal disease such as HIV-infected patients with functional or anatomic asplenia, complement deficiencies, travel exposure, college students living in dormitories, or military recruits[81].

Poliovirus vaccine

In 1988, all member states of the World Health Organization voted to launch a global goal to eradicate polio. At that time, wild poliovirus was endemic in more than 125 countries on five continents, paralyzing more than 1000 children every day. As a result of the Global Polio Eradication Initiative, by the end of 2006 only four countries remained which had never interrupted endemic transmission of wild poliovirus (Nigeria, India, Pakistan and Afghanistan). In 2006, fewer than 2000 cases were reported[83,84]. Since humans are the only known reservoir of poliovirus, eradication through immunization programs hopefully will be possible in the future.

Two different kinds of polio vaccine are available: a live attenuated (weakened) oral polio vaccine (OPV) and an inactivated (killed) polio vaccine (IPV). Following OPV vaccination, immunocompromised persons are at greater risk of developing vaccine-associated paralytic polio than healthy individuals; therefore OPV is contraindicated for HIV-infected persons. In developing countries where HIV infection is endemic and the risk of infection with wild-type poliomyelitis virus is high, the benefits of immunization outweigh the apparently low risk of paralysis due to vaccination with OPV[85]. However, OPV is no longer routinely available in western countries, having been replaced with the inactivated vaccine for routine infant and childhood immunization[2,11]. All adults who are unvaccinated or whose vaccination status is not documented, including those with HIV, should receive a primary vaccination series with IPV. This consists of two doses of IPV at 4-8 week intervals and a third dose 6-12 months after the second dose[86]. Boosting of poliovirus antibody titres was demonstrated in seropositive HIV-infected adults with a history of childhood vaccination, following one dose of IPV[24]. A single lifetime booster with IPV is recommended for all adults at risk of exposure to polio (mainly through travel to endemic zones such as many parts of Africa and Asia), although the duration of protection is unknown[86,87].

Papillomavirus

Persistent viral infection with oncogenic types of human papillomavirus (HPV) leads to cancer of the cervix, anus, vagina, vulva or penis. Cervical cancer incidence and deaths have substantially decreased in countries with organized cervical cancer screening programs. However, despite this success, cervical cancer is the second most common malignancy among women and a leading cause of cancer death worldwide. Among individuals with HIV-infection, coinfection with HPV causes significant cancer-related morbidity and mortality[88]. Vaccines that prevent these persistent HPV infections have the potential to further reduce the burden of disease[89,90].

There are over 100 genotypes of HPV. About 70% of cervical cancers are caused by types 16 and 18[91]. Less virulent forms of HPV (types 6 and 11) are associated with low-grade cervical abnormalities and 90% of genital warts[92].

Two HPV vaccines (bivalent HPV 16/18 and quadrivalent HPV 6/11/16/18 vaccine) have been recently developed. Clinical trials of the HPV vaccines suggest high efficacy and an excellent safety profile in women who do not have abnormal cervical cytology or HPV infection prior to immunization. However women with HIV or other immunosuppressive conditions were not enrolled in the main HPV vaccine trials and its efficacy and safety in this setting remains unknown[93]. The HPV vaccines will likely have a significant impact on HPV-related disease in immunocompetent individuals. It remains to be seen what impact these vaccine will have on those severely immunodepressed.

The American Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of females aged 11-12 years with three doses of quadrivalent HPV vaccine. Vaccination also is recommended for females aged 13-26 years who have not been previously vaccinated or who have not completed the full series. Females who have not been infected with any of the HPV vaccine types would receive full benefit from vaccination. Vaccination would provide less benefit to females if they have already been infected with one or more of the four vaccine HPV types[94]. Those women who are HIV infected might follow these recommendations since HPV vaccines are inactive and severe side effects are not expected. Cervical cancer

screening recommendations should not change for females who receive HPV vaccine. Furthermore, a higher frequency of gynecologic follow-up and cervical cancer screening among HIV-infected women is desirable since gynecologic care among well-followed HIV-positive women is poor and needs to be improved[95].

Men who have sex with men and HIV-infected males may be at high risk for anal cancer, but to date HPV vaccine is not licensed for use among males. Studies of male vaccination to prevent HPV-associated cancers occurring in men are underway[94].

Live vaccines

Measles, mumps and rubella vaccine

There is no evidence to suggest that mumps or rubella infections are more severe in the HIV setting. The most important consequences of rubella are miscarriages, stillbirths, and fetal anomalies that result when rubella infection occurs during early pregnancy, especially during the first trimester. Conversely, HIV-infected persons are at increased risk for severe complications if infected with measles.

The great majority of HIV-infected adults from western countries are seropositive to measles[96]. Nevertheless, insufficient uptake of measles, mumps, and rubella (MMR) vaccine in several European countries in recent years has led to localized measles, mumps and rubella outbreaks, and endemic measles could reappear[11,97]. Recently, mumps outbreaks have been reported in the UK, Canada and the USA, probably related to low effectiveness of different vaccine strains[98]. The HIV-infected patients from developed regions are also at risk while travelling abroad since measles, mumps and rubella remain common diseases in many countries of the world.

The MMR vaccine response in measles-seronegative HIV-infected adults is poor[96]. Seroconversion rates for rubella are also diminished in these patients. Immune reconstitution is likely to improve seroconversion rates[11]. Another concern is the theoretical risk of severe complications with vaccine strain measles. However, among HIV-infected persons who did not have evidence of severe immunosuppression, no serious or unusual adverse events have been reported after MMR vaccination[11,99].

The MMR vaccine is recommended for all asymptomatic or mildly symptomatic HIV-infected persons who are not severely immunosuppressed (CD4+ T-cell < 200 cells/mm^3 for adults) and who lack evidence of measles immunity[11,99]. Those HIV-infected women of child-bearing age should be also screened for rubella IgG and MMR vaccine should be given to rubella-seronegative women with CD4+ T-cell counts > 200 cells/mm^3 in order to avoid congenital rubella syndrome[11]. Severely immunocompromised patients and other symptomatic HIV-infected patients who are exposed to measles should receive immune globulin prophylaxis regardless of vaccination status because they may not be protected by the vaccine[99].

No specific recommendations have been made about measles-seropositive HIV-infected adults without immunity to mumps or rubella (excluding women of child-bearing age). According to recommended adult immunization schedules, all adults should be immune to these diseases and therefore seronegative adults should be vaccinated unless they have a medical contraindication such as severe immunosuppression or pregnancy. The MMR vaccine, single mumps, or single rubella vaccine may be administered in this context.

Varicella vaccine

Patients with HIV infection are at risk for developing severe illness from either varicella or zoster. Recent ACIP recommendations include routine varicella vaccination of all healthy persons aged > 13 years without evidence of immunity, and varicella vaccination for HIV-infected adolescents and adults with CD4+ T-cell counts ≥ 200 cells/mm^3 should be considered[100]. In this circumstance the vaccine is regarded as safe. British guidelines are more conservative and recommend varicella vaccination, after weighing potential risks and benefits, for varicella IgG seronegative asymptomatic HIV-infected adults who have CD4+ T-cell counts > 400 cells/mm^3 and to consider vaccination for asymptomatic HIV-infected patients with CD4+ T-cell counts < 400 cell/mm^3 but > 200 cell/mm^3 while on stable HAART. If vaccination of HIV-infected persons results in clinical disease, the use of acyclovir might modify the severity of disease. Data on the efficacy of varicella vaccine in HIV-infected adolescents and adults are still scarce[11].

On May 25, 2006, the FDA licensed the zoster vaccine for the prevention of herpes zoster in persons 60 years of age or older that contains significantly higher titers of live attenuated virus than standard available varicella-containing vaccines. Therefore, this zoster vaccination is contraindicated in HIV-infected people[101].

Other live vaccines

Administering tuberculosis bacilli Calmette-Guérin (BCG) vaccine to HIV-infected persons is absolutely contraindicated because of its potential to cause disseminated disease, regardless of CD4+ T-cell count and clinical status, even if the risk of acquiring tuberculosis is high[2]. Also, BCG is contraindicated in per-

sons suspected to be HIV positive, regardless of clinical status[11].

The smallpox vaccine is a live vaccine that contains not the smallpox virus itself, but another virus known as the vaccinia virus. Immunocompromised patients are at increased risk for severe adverse events. Therefore smallpox vaccine is contraindicated in HIV infection in most of cases, with very rare exceptions such as personnel working with orthopox viruses[102,103].

Three other live vaccines are usually travel medicine-related immunizations and have inactivated alternatives available. Inactivated (killed) poliovirus vaccine and inactivated parenteral typhoid vaccine should be used instead of oral (live) poliovirus and the live-attenuated oral typhoid vaccine, respectively[2]. The new inactivated oral cholera vaccine should be used instead of prior attenuated oral or inactivated parenteral cholera vaccines[87].

Finally, yellow fever vaccine is a live-virus vaccine and has the potential for causing adverse events in immunocompromised individuals, including those with HIV infection, mainly in older people. Its use in patients with HIV remains controversial, but its efficacy and safety in patients with CD4+ T-cell counts > 200 cells/mm^3 have been demonstrated[104]. Yellow fever is a potentially fatal infection endemic in various tropical areas in Africa and America, and a number of countries require an international certificate of vaccination for entry. This vaccine should be offered to patients with CD4+ T-cell counts > 200 cells/mm^3 who are due to travel to countries in which there is a risk of exposure to yellow fever infection after appropriate counseling of the risks[87,104]. Medical letters of exemption can be written for patients with contraindications to live attenuated vaccine.

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