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Strategies to increase responsiveness to hepatitis B vaccination in adults with HIV-1

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Abstract

HIV and hepatitis B virus co-infection leads to substantially increased morbidity and mortality compared with either infection alone. Immunisation with hepatitis B virus vaccine is the most effective way to prevent the infection in people with HIV; however, these patients have decreased vaccine responses and a short duration of protection compared with immunocompetent individuals. Control of HIV replication with highly active antiretroviral therapy and increased CD4 cell counts are associated with improved immune responses to hepatitis B vaccination. New vaccination strategies, such as increased vaccine dose, use of the intradermal route, and addition of adjuvants, could improve response rates in adults with HIV.

Introduction

Infection with hepatitis B virus in people with HIV is a preventable problem of global importance. People at risk for HIV infection are also at risk for hepatitis B infection because the viruses have similar routes of transmission. An estimated 10% of the 34 million people infected with HIV worldwide have chronic hepatitis B infection.[1,2] The prevalence of co-infection varies by geographical region and risk factors for transmission. In people with HIV in western Europe and the USA, the prevalence of chronic hepatitis B infection is highest in men who have sex with men and injection drug users.[1] In the US HIV Outpatient Study cohort,[3] between 1996 and 2007, the overall prevalence of co-infection with hepatitis B was 8·4%, which was 20 times that of the general US population. In another US study between 1998 and 2001,[4] the incidence of acute infection with hepatitis B was 12·2 cases per 1000 person-years in patients with HIV receiving care, which was 370 times that in the general population. In countries where highly active antiretroviral therapy (HAART) is widely available, deaths from AIDS-related causes have fallen, but liver disease has emerged as one

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JAW and NGR were responsible for the design of this Review. JAW did the primary writing of the Review, with substantial contributions from NGR, SE, LL, and MJM. All authors contributed to revisions and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

of the main causes of morbidity and mortality.[5-7] HIV infection adversely affects all phases of hepatitis B infection, increasing the risk of chronic infection, decreasing the rate of hepatitis B e antigen clearance, increasing virus replication, accelerating the loss of hepatitis B surface antibody, and increasing the risk for cirrhosis and hepatocellular carcinoma.[8] Men infected with both HIV and hepatitis B have liver-related mortality that is eight times higher than that in men with HIV alone and 17 times higher than in those with hepatitis B alone.[9]

Because of the increased incidence of hepatitis B infection in people with HIV and the effect of co-infection on morbidity and mortality, all hepatitis B-susceptible individuals with HIV infection should be vaccinated against hepatitis B. The US Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents released by the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and HIV Medical Association,[10] and the US Advisory Committee on Immunization Practices,[11] the European AIDS Clinical Society,[12,13] and the British HIV Association[14] all recommend that all individuals with HIV who are susceptible to hepatitis B should be vaccinated with the primary vaccine series— typically three doses given during a 6 month period. However, in the US HIV Outpatient Study cohort at nine HIV outpatient clinic sites, only 32% of eligible patients received at least one dose of vaccine. Only 53% of those who received one dose of vaccine completed the series, and of these, only 37% achieved protective antibody titres.[15] In immunocompetent individuals, more than 95% of infants and children and more than 90% of adults achieve protective hepatitis B surface antibody (anti-HBs) titres after completion of the recommended primary vaccine series.[16] Immunocompromising illnesses, chronic kidney disease,[17-21] diabetes mellitus,[22,23] male sex, older age,[24] obesity, and some HLA types[25,26] are associated with low hepatitis B vaccine responses.[27-29] In particular, HIV-infected individuals achieve protective anti-HBs titres in only 18–71% of cases after completion of the standard-dose primary vaccine series.[15,30-38] Increased antigen dose and number of vaccinations, alternative vaccination routes (ie, intradermal), or addition of an adjuvant could increase response rates.

In this Review, we aim to compare the NIH, CDC, and HIV Medical Association, and the European AIDS Clinical Society and British HIV Association guidelines for vaccination against hepatitis B in adults with HIV (table 1), provide a definitive review of vaccination studies in these patients, assess the factors associated with improved vaccine response, and provide a comprehensive review of alternative vaccination strategies to improve vaccine response rates.

Guidelines for hepatitis B vaccination in adults with HIV

All three guidelines recommend screening for hepatitis B in people with HIV but differ in their recommendations for when and how to vaccinate (table 1).

Although the US guidelines do not specifically endorse high-dose hepatitis B vaccination, they do note that the 40 μg dose can be considered for the primary immunisation in all individuals with HIV infection. The guidelines note that “additional studies are needed to determine optimal vaccine strategies in individuals with advanced immunosuppression”. No clear recommendation exists for annual testing of anti-HBs amounts and booster

vaccination, but some experts recommend yearly checks of anti-HBs titres in individuals at high risk for hepatitis B acquisition.[10]

The 2011 European AIDS Clinical Society guidelines for the clinical management and treatment of chronic hepatitis B or C co-infections in adults with HIV infection also recommend that these adults are screened for existing or past hepatitis B infection. Vaccination is recommended for all patients with HIV infection who do not have HBsAg or anti-HBs antibodies (irrespective of their CD4 cell count). The guidelines also recommend consideration of revaccination for individuals with anti-HBs titres lower than 10 IU per L.

The 2008 British HIV Association guidelines recommend that all HIV-infected adults should be screened for evidence of present or past hepatitis B infection, and suggest hepatitis B vaccination for all non-immune or non-infected adults. They recommend both standard (0, 1, and 6 months) and alternative (0, 1, 2, and 12 months) schedules, but do not generally recommend intradermal vaccination. The guidelines suggest that anti-HBs titres should be measured 6–8 weeks after vaccination, and recipients with anti-HBs lower than 10 IU per L should be offered three additional double doses, given at monthly intervals. Depending on the degree of risk, these guidelines recommend that annual anti-HBs concentrations should be measured and a booster offered to individuals whose anti-HBs concentrations have de creased to less than 10 IU per L.

It is evident that these societies' guidelines do vary somewhat. To understand the basis for these recommendations, we should first review data for correlates of protection and duration of protection provided by the hepatitis B vaccine.

Correlates of protection and duration of protection

The first hepatitis B vaccines became commercially available in 1982 and were created by harvest of HBsAg from the plasma of patients with chronic infection. Recombinant DNA technology has permitted the production of large quantities of safe and effective hepatitis B vaccines since 1986, which are used in most countries. A recombinant vaccine was created by insertion of the *HBsAg* gene into an expression vector that could direct the synthesis of large quantities of HBsAg in *Saccharomyces cerevisiae.* Hepatitis B virus vaccines contain 10–40 μg of HBsAg protein per mL and aluminium phosphate or aluminium hydroxide adjuvant, depending on the manufacturer.[39] The recommended dose of HBsAg varies by vaccine manufacturer (table 2) and is usually given on a 0, 1, and 6 months schedule. If more rapid protection is needed—eg, for travellers or after exposure to hepatitis B virus—three doses can be given in a 0, 1, and 2 months accelerated schedule, followed by a booster at 12 months. In 1991, WHO recommended that the hepatitis B vaccine be introduced into the expanded programme on immunisation, and all countries were asked to create a universal immunisation programme, either in infancy or adolescence, by 1997.[41]

The established correlate of protection for hepatitis B vaccination is an anti-HBs antibody titre of 10 IU per L or higher. Immunocompetent individuals who achieve this titre after vaccination have almost complete protection against acute and chronic hepatitis B infection.[42-44] Individuals with HIV who are non-responders to vaccine (anti-HBs antibody concentrations <10 IU/L) do not seem to be protected from infection because they have

similar rates of hepatitis B infection as unvaccinated individuals with HIV.[45] Two mechanisms mediate the protection provided by hepatitis B vaccination: immediate virus neutralisation by anti-HBs antibodies and activation of specific memory CD4 T cells that will promote subsequent activation of memory B cells and the secretion of additional anti-HBs antibodies.[27]

The duration of protection provided by the hepatitis B vaccine in immunocompetent individuals is not completely understood, and there are even fewer data for the duration of protection in people with HIV. Anti-HBs antibody titres decrease over time and can fall below protective concentrations. Several studies have shown that peak antibody titre 1 month after completion of the vaccination series is associated with the longevity of protective antibody titres in healthy adults.[46-48] Investigators developed a mathematical model for anti-HBs antibody decay on the basis of a cohort of recombinant vaccine recipients (none of whom were tested for HIV) who were followed up for 10 years; the model was validated on a different set of vaccine recipients. Anti-HBs antibody titres 60 days after completion of the vaccine series could predict titres several years later.[49] The extent of the maximum antibody response after vaccination strongly predicted the persistence of protective antibody in a long-term immunogenicity and efficacy study in homosexual men; however, the risk of infection with hepatitis B virus increased substantially when anti-HBs antibody titres fell below 10 IU/L.[50] In a follow-up study of immunocompetent Native Alaskans who had received the plasma-derived hepatitis B vaccine when they were older than 6 months and had a documented response, 60% had anti-HBs antibody titres of 10 IU per L or higher 22 years later. Of those who did not have protective titres, 77% responded to a booster, with an anti-HBs titre of 10 IU per L or higher at 10–14 days after the booster, and 81% had protective anti-HBs concentrations by 60 days after the booster.[51] Similar findings were noted in a 20 year follow up study of Thai infants who had received the recombinant hepatitis B vaccine.[52] A meta-analysis that examined the duration of protection provided by the hepatitis B vaccine in 22 studies with 11 090 participants noted that long-term protection is sufficient to prevent infection in immunocompetent individuals for at least 20 years.[53] However, because of a paucity of data, no such conclusions can be made for immunocompromised individuals.

The US Military HIV Natural History Study cohort reported that attainment of the protective concentration of anti-HBs antibody (but not the number of doses of vaccine) was associated with reduced risk of infection and reduced development of chronic hepatitis B infection.[54] Additionally, the investigators reported that patients who developed an initial response to the vaccine derived benefit from vaccination for at least 7 years.[54] In Rey and colleagues'[30] small prospective study, 58% of participants with HIV infection had protective anti-HBs titres 12 months after receiving a standard dose of hepatitis B vaccine. In a prospective study of high-dose vaccine (Recombivax 40 μg) in individuals with HIV infection, 60% of participants responded to the primary vaccine series and 89% responded after one, two, or three boosters, 63% of responders to the vaccine series had protective titres at 12 months, and 33% had protective titres at 24 months.[55]

Why do people with HIV have lower rates of seroconversion, lower peak anti-HBs titres, and accelerated decreases in protective antibody titres? B cell dysfunction has been

described in HIV infection, including lower peripheral B cell counts, increased numbers of activated and exhausted B cells, increased numbers of immature transitional B cells in circulation, hypergammaglobulinaemia, and decreased numbers of memory B cells.[56-58] B-cell dysfunction can lead to diminished antibody responses and accelerate the loss of antigen-specific memory B cells in people with HIV.[59] Work in adolescents with HIV showed low frequencies of hepatitis B virus-specific memory B cells, changed phenotypes, and reduced proliferation after vaccination.[60] The detection of anti-HBs titres of 10 IU per L or higher was associated with higher numbers of hepatitis B-specific memory B cells per 100 000 peripheral blood mononuclear cells.[60] B-cell numbers increase after HAART; however, improvement might be limited to those who are treated early in the course of HIV disease.[58] Other studies have proposed that the poor response to hepatitis B vaccine could be due to impaired T-cell activation.[61] The number of T regulatory cells is often higher in individuals with HIV than in healthy donors,[62] and is independently associated with non-responsiveness to hepatitis B vaccine in individuals with HIV.[63] T regulatory cells inhibit B cell proliferation by directly inducing apoptosis of proliferating B cells.[64]

In immunocompetent people, B-cell and T-cell immune memory persists after the time when anti-HBs titres might no longer be detectable.[65-69] Upon exposure to hepatitis B virus, this memory leads to a vigorous anamnestic response, which prevents acute infection and chronic disease.[65-69] On the basis of results confirming immune memory in healthy individuals, the CDC has recommended that no booster dose should be given to fully vaccinated healthy people.[70,71] However, in immunocompromised individuals, such as dialysis patients, only half of the patients with anti-HBs lower than 10 IU per L develop an anamnestic response to booster doses, which suggests poor immunological memory.[72] In two studies in adults with HIV (with isolated anti-hepatitis B core antibodies), investigators reported anamnestic response rates (defined as anti-HBs titre ≥10 IU/L 2 weeks after one vaccine) of 32%[73] and 24%.[74] More research is needed to assess the anamnestic response in adults with HIV without existing anti-hepatitis B core antibodies, who are vaccinated against hepatitis B and have anti-HBs antibody concentrations lower than 10 IU per L. Whereas in im munocompetent individuals, persistence of anti-HBs at a concentration of 10 IU per L or higher has been deemed not necessary for protection because of persistence of immune memory,[71] no data exist to support such a statement for immunocompromised individuals, including those with HIV.

Another potential challenge in prevention of hepatitis B with vaccination is the development of vaccine-escape mutants.[75-78] Mutations in the viral surface protein can lead to a change in the surface antigen, such that antibodies directed at the surface antigen protein (induced by HBsAg vaccines) do not neutralise the mutants. Therefore, people who have been vaccinated against hepatitis B and have protective anti-HBs titres could still be infected by vaccine-escape mutants. The mutants can develop as a result of selective pressure from nucleoside or nucleotide analogue treatment for chronic hepatitis B (particularly lamivudine mono therapy) and HIV. This antiviral pressure has led to mutations in the HBsAg protein, some of which have been associated with antiviral drug-associated potential vaccine-escape mutants.[76] However, there has been very little documented transmission of these mutants[78] and more studies are needed to assess their clinical and epidemiological importance.[78]

Hepatitis B vaccine efficacy: effect of patient factors

Various factors, such as HAART, CD4 cell count, and viral load, either alone or in combination, can affect efficacy of hepatitis B vaccine in patients with HIV.

The efficacy of the standard-dose hepatitis B vaccine in adults with HIV in the era of HAART ranges from 18 to 71% (table 3).[15,30-38] Overton and colleagues[31] reported the lowest vaccine efficacy of 18% in their study, in which most participants received less than the recommended standard dose of Engerix-B (10 μg instead of the recommended 20 μg). Additionally, Landrum and colleagues[36] noted a low vaccine efficacy of 35% in their study, in which they reviewed vaccination data between 1988 and 2005; 49% of participants received their first vaccine before 1996 (before the era of HAART), and only 33% were on HAART at the time of the last vaccination.

In general, there seems to be an association between high CD4 cell counts at the time of vaccination and anti-HBs seroconversion rates, for both standard-dose vaccination[15,30,32,33,37,38] and double-dose vaccination[55,79-81,85] (table 3). However, in some studies, the investigators reported no association between CD4 cell counts and anti-HBs seroconversion rates when they included HIV viral load or receipt of HAART in multivariable analyses.[31,35,36,83,85] Therefore, in individuals with low CD4 cell counts, vaccine response might be improved by suppressed HIV replication.

Many studies have shown an association between low or undetectable viral load of HIV and anti-HBs seroconversion rates for either standard-dose[15,31,34,35,38] or double-dose vaccinations.[55,79,82-85] In the studies in which no association was shown, viral load was either not assessed,[30,80] was not included in the final multivariable model,[36] or the median viral load was uniformly lower than 50 copies per mL.[32,33] Investigators reported no association between viral load and vaccine responsiveness in two studies,[37,81] and noted high mean or median HIV viral loads (52 556–75 187 copies per mL) in both. Whether there were adequate numbers of individuals with suppressed viral loads in these studies to detect an association is unknown.

Patients with a combination of high CD4 cell count and suppressed HIV replication have the best responses to hepatitis B vaccination. In a large US military cohort, 62% of individuals with HIV infection on HAART with HIV RNA less than 400 copies per mL and a CD4 count of 350 cells per μL or higher achieved anti-HBs titres above 10 IU/L. In patients with CD4 counts of 350 cells per μL or higher, those who were not on HAART had low odds of developing a vaccine response (odds ratio 0·47, 95% CI 0·30–0·70).[36] In a prospective study by Paitoonpong and Suankratay, in which all participants were on HAART and had HIV viral loads lower than 50 copies per mL, those who responded with protective titres had higher mean CD4 cell counts than did the non-responders (p=0·035). Additionally, 57% of participants had anti-HBs titres of 100 IU/L, which are associated with long-term protection.[33]

Ongoing HIV viraemia might decrease the likelihood of a successful immune response to hepatitis B vaccination. The US, British, and European guidelines do not recommend delay of vaccination in individuals with HIV until virological suppression is achieved; however,

the European guidelines do recommend that HAART is started before administration of hepatitis B vaccine for individuals with CD4 cell counts lower than 200 cells per μL. The health-care practitioner should always weigh up the risk of vaccination delay and the likelihood of acute hepatitis B infection in patients when making decisions to postpone vaccination until HAART is started and virological suppression is achieved. Whether or not the selected HAART regimen contains an active agent against hepatitis B might also affect this judgment.[86] A reasonable approach for individuals who have not responded to the primary vaccine series is to start HAART and wait for virological suppression, and perhaps even a sustained increase in CD4 cell count, before revaccination is offered. New approaches are needed to improve immunogenicity to hepatitis B vaccination in people with HIV.

Repeat vaccination for non-responders

When patients with HIV do not respond to the primary hepatitis B vaccine series, several strategies are available. British and US guidelines suggest delaying repeat vaccination until viral suppression has been achieved.[10,14] The percentage of initial non-responders who responded to a second series of vaccine doses ranged from 36 to 85% (table 4).[30,37,55,87-89] Revaccination seems to be an appropriate strategy for non-responders to the initial vaccine series. However, in Bloom and colleagues'[88] retrospective study, only 44% of the initial vaccine nonresponders at one of their study sites had repeat vaccination. Similar to the primary vaccination series, anti-HBs titres should be checked 1-2 months after completion of the revaccination series.

No randomised controlled trials have compared repeat vaccination with standard-dose versus double-dose vaccination (table 4). In one study,[89] the investigators recorded a higher response rate in people who received double-dose vaccination (85%) than in those who received standard-dose vaccination (59%; p=0·006). The multivariate analysis of this study showed that use of HAART, CD4 cell count of 200 cells per μL or higher, and receipt of double-dose vaccination were all notable predictors of vaccine response.[89] Other revaccination studies noted that CD4 cell count,[38] female sex,[87] age,[87] and HIV viral load[87] were independent predictors of vaccine response.

Although non-responders to the primary series might develop protective anti-HBs concentrations after repeat vaccination (1-2 months after vaccination, at the time of peak titres), there is a concern that their protective antibodies could diminish more quickly. Cruciani and colleagues[55] reported that the group of non-responders to the primary vaccination cycle who responded to revaccination lost protective antibody concentrations faster than did those patients who responded after the first vaccination cycle (p=0·037). Rey and colleagues[30] noted a shorter maintenance of protective anti-HBs antibody titres at 12 months in patients who were revaccinated with a series of three additional doses (55%) than in those who responded to the initial vaccine series (90%).

Strategies to improve vaccine efficacy

New vaccination strategies, such as increased hepatitis B vaccine doses, intradermal vaccination, and adjuvanted vaccines, improve immunogenicity to vaccine in adults with

HIV. A fundamental strategy to improve efficacy is to ensure that patients receive the complete series of vaccine. Receipt of three or more doses of vaccine was associated with increased anti-HBs seroconverters in the US Military HIV Natural History Study cohort; however, only 62% of participants received three or more doses.[36] Data are scarce for factors associated with the successful completion of the hepatitis B vaccine series in HIV-infected adults, a group that is by no means homogeneous. Tedaldi and colleagues[15] noted in multivariate analysis that an increase in the number of visits per year with HIV care providers was associated with receipt of at least one hepatitis B vaccine, as was the classification of the patient as high-risk heterosexual versus men who have sex with men. These findings might suggest that providers are more likely to provide vaccination for patients they deem higher risk for acquisition, rather than characteristics associated with vaccine uptake. In general, systems-based checks increase rates of hepatitis B vaccine series completion. The implementation of a nurse programme for vaccination at one of the Swiss HIV Cohort clinics significantly increased the proportion of clinic patients with hepatitis B immunity from 32% to 76% over a 3 year period compared with the control group clinics, where the increase was only from 33% to 39% ($p < 0{\cdot}001$).[90] A specific hepatitis B vaccination form that was placed in patients' charts led to increased vaccination series completion from 67% to 79% in one British outpatient HIV clinic.[91] As electronic medical records become more widespread, system checks and electronic reminders could facilitate an increase in series completion rates. Further exploration of reasons for non-completion of vaccine series and the implementation of systems-based approaches to increase completion rates are the first steps that should be taken to improve vaccine responses.

Increased HBsAg dose has been investigated as a strategy to improve immunogenicity to hepatitis B vaccines. Double-dose (40 μg) hepatitis B vaccination is recommended for patients receiving haemodialysis.[11] The role of a double dose has been examined in several studies in adults with HIV (table 3).[55,79-81,83-85] Randomised controlled trials that compared high-dose and standard-dose vaccines reported mixed results.[79,81,84] Studies that compared three doses of high-dose with standard-dose vaccine did not report statistically significantly higher serocon version rates,[79,83] except in a subgroup of patients with CD4 counts of 350 cells per μL or higher or HIV RNA less than 10 000 copies per mL.[79] However, in their study, Launay and colleagues[84] reported significantly higher sero conversion rates for high-dose GenHevac-B 40 μg given in four doses at 0, 1, 2, and 6 months compared with GenHevac-B 20 μg given as three doses at 0, 1, and 6 months (82% *vs* 65%, $p < 0{\cdot}001$).[84] Other implications from this study are that the doubledose vaccine group had vaccine responses independent of age and the greatest percentage of responders with titres of at least 100 IU per L (74%),[84] which has been associated with long-term duration of protection.[50] Potsch and colleagues reported similar findings,[85] since they noted significantly higher vaccine response rates in patients who received four doses of hepatitis B vaccine at 0, 1, 2, and 6 months, than in those who received three doses of vaccine at 0, 1, and 2 months.

An alternative vaccine delivery method, the intradermal route, has shown improved immunogenicity in patients with chronic kidney disease.[92] Similarly, in patients with HIV, the intradermal route was more immunogenic than was standard intramuscular delivery. In Launay and colleagues'[84] study, intradermal vaccine recipients (GenHevac B 4 μg × four

doses) had significantly better seroconversion rates (77%) compared with the standard dose group (GenHevac B 20 μg × three doses; 65%, p=0·02). Intradermal delivery could permit vaccine dose sparing, because only 20% of the antigen dose has elicited better vaccine responses than the full standard intramuscular dose, which could be important in resource-limited settings if the cost of the vaccine is a restrictive factor in vaccination.

The available licensed hepatitis B vaccines contain aluminium adjuvants. Other adjuvants, such as cytokines and other compounds, have been tested in human beings to try to improve responses (table 5). Only two adjuvants other than aluminium, granulocyte macrophage colony-stimulating factor (GM-CSF) and CPG 7909 (oligodeoxynucleotide-containing CpG motif, Toll-like receptor 9 agonist), have been tested in combination with hepatitis B vaccines in people with HIV. Use of GM-CSF as an adjuvant to double-dose vaccine has shown disparate results, despite similar median CD4 cell counts of participants in the studies.[93,94] A new adjuvant immunostimulatory DNA sequence, CPG 7909, plus Engerix-B vaccine given to individuals with HIV resulted in a higher proportion of participants achieving and regaining seroprotection—geometric mean anti-HBs titres were higher at all time points up to 60 months in the adjuvanted vaccine group.[95] Another immunostimulatory DNA sequence adjuvant, ISS 1018 (oligodeoxyribonucleotide-containing CpG motif), combined with 20 μg HBsAg (HEPLISAV, Dynavax Technologies, CA, USA) given at 0, 8, and 24 weeks elicited a better rate of seroconversion than did 20 μg HBsAg vaccine given at 0, 4, and 24 weeks in healthy adults aged 40–70 years.[96]

The oil-in-water adjuvants AS02 (GlaxoSmithKline Biologicals [GSK], Rixensart, Belgium), which contains 3-*O*-descayl-4′-monophosphoryl lipid A (MPL) and QS21 (immunostimulant extracted from the bark of the *Quillaja saponaria* tree), and AS04 (GSK), which contains MPL and aluminium phosphate, have been combined with hepatitis B vaccines and tested in adults with chronic kidney disease (table 5). FENDrix (GSK), which contains 20 μg recombinant HBsAg plus AS04, has elicited higher seroconversion rates, higher anti-HBs titres, and longer seroconversion than four double doses of standard vaccine in patients with renal insufficiency.[97,99-101] FENDrix was licensed in Europe in 2005 for people with renal insufficiency (predialysis and haemodialysis patients) older than 15 years. AS02-adjuvanted hepatitis B vaccine has been studied in patients with renal insufficiency and resulted in higher rates of seroconversion and anti-HBs titres than those of unadjuvanted vaccine.[98]

Future research needs and conclusions

People with HIV have decreased antibody responses to hepatitis B vaccination, and their titres of protective antibodies decrease more rapidly than those of immuno-competent individuals, possibly because of B-cell dysfunction caused by HIV infection. Control of HIV replication (as shown by low or undetectable viral loads), receipt of HAART, and higher CD4 cell counts, improve seroconversion rates in people with HIV (tables 3 and 4). Additionally, a higher dose hepatitis B vaccine,[79,83,84] intradermal vaccination,[84] and vaccine adjuvanted with CPG 7909[95] improve seroconversion rates in adults with HIV. Vaccines adjuvanted with ISS 1019, AS02, and AS04 can increase rates of seroconversion in other immuno-compromised populations, such as older adults and those with renal

insufficiency. Additional studies of adjuvants in people with HIV are needed. The duration of protection provided by hepatitis B vaccination in people with HIV is unclear. Although immunocompetent individuals have protective immune memory responses to hepatitis B at anti-HBs concentrations lower than 10 IU per L,[65-69] no such data exist for people with HIV. Further investigation into the duration of immune memory and anamnestic responses to booster doses in adults with HIV who have received the vaccine is warranted. More research about why people with HIV have decreased immune responses and immune memory to vaccines could lead to the development of more effective vaccines for this population. With data suggesting that high-dose hepatitis B vaccine and intradermal (dose-sparing) vaccines improve seroconversion rates, a study of the cost-effectiveness of these strategies would help to promote their widespread use. Steps should be taken to ensure that all individuals with HIV receive the standard of care in hepatitis B vaccination. All people with HIV should be screened for hepatitis B infection and immunity and vaccinated if they do not have immunity and are not infected. They should also have documented post-vaccination titres and undergo revaccination if they did not respond to the primary vaccine series. Implementation of the standards of care can go a long way towards prevention of the compounded problem of HIV and hepatitis B co-infection, which causes high morbidity and mortality. However, only with further investigation will we be able to design vaccines and vaccination strategies that are highly effective in prevention of the acquisition of hepatitis B virus co-infection in individuals with HIV.

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Search strategy and selection criteria

References for this Review were identified from searches of PubMed for articles published between January, 1971 and August, 2012, with use of combinations of the terms “hepatitis B”, “vaccination”, “immune memory”, “immunogenicity”, “vaccine response”, “adjuvant”, and “HIV.” Articles obtained from these searches and relevant references cited in those articles were reviewed. Articles published in English and French were included. Studies of hepatitis B vaccine efficacy in adults with HIV-1 that were done before the era of HAART were not included in the tables or discussion of hepatitis B vaccine efficacy in adults with HIV-1 infection.

Table 1
Summary of guidelines for HBV vaccination in adults with HIV

	US 2009[10] (NIH/CDC/HIVMA*)	European 2011[12,13] (EACS†)	British 2008[14] (BHIVA‡)
Test all for evidence of HBV infection and immunity and vaccinate if indicated	Yes	Yes	Yes
Isolated hepatitis B core antibody (anti-HBc)	Vaccinate with primary series	Give one vaccine dose and check anti-HBs 2-4 weeks later; if anti-HBs <10 IU/L, consider a full course of vaccination	Management is controversial; could give one vaccine dose and check anti-HBs 2 weeks later; if anti-HBs <10 IU/L, then give two additional doses
CD4 cell count at time of vaccine initiation	Do not delay until target CD4 count is reached, but it is best to vaccinate when CD4 cell count ≥350 cells per μL	Offer vaccination irrespective of CD4 cell count; however, HAART should be started before vaccination for individuals with CD4 cell count ≤200 cells per μL and ongoing HIV viral replication	No recommendation
When to check anti-HBs after completing vaccination series	1 month	..	6-8 weeks; vaccine recipients with anti-HBs >10 but <100 IU/L should be offered one additional vaccine dose
What to do for non-responders (those with anti-HBs ≤10 IU/L after completion of vaccine series)	Consider revaccination; "Certain specialists might delay revaccination until after a sustained increase in CD4 count is achieved on ART"	Consider revaccination	Revaccinate with three high doses (40 μg) given at monthly intervals; depending of level of risk, can delay revaccination until CD4 cell count >500 cells per μL
Recommendation for high dose (40 μg HBsAg)	No definite recommendation; for vaccine non-responders "certain specialists recommend… revaccination with 40 μg doses"	No definite recommendation; "Consider double dose (40 μg) and intradermal vaccination in non-responders, in particular with low CD4 and high viremia"	Give high dose for non-responders to vaccine series
Recommendation for periodic testing of anti-HBs in people who complete the vaccine series	No recommendation; "Certain specialists suggest once yearly assessments for patients who have an ongoing risk for HBV acquisition, as recommended for dialysis patients"	No recommendation	Measure anti-HBs yearly; offer a booster to people with anti-HBs <10 IU/L and ideally <100 IU/L

HBV=hepatitis B virus. NIH=National Institutes of Health. CDC=Centers for Disease Control and Prevention. HIVMA=HIV Medical Association. EACS=European AIDS Clinical Society. BHIVA=British HIV Association. HAART=highly active antiretroviral therapy. ART=antiretroviral therapy.

*US Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents released by the NIH, CDC, and HIVMA.

†EACS Guidelines.

‡BHIVA Guidelines for Immunisation of HIV-infected Adults.

Table 2
Recombinant hepatitis B vaccines available internationally

	Manufacturer	Country of production	Recommended dose of HBsAg for adults*
Engerix-B	GlaxoSmithKline	Belgium	20 μg†
Twinrix	GlaxoSmithKline	Belgium	20 μg‡
Recombivax HB	Merck	USA	10 μg§
HBVAXPRO	Sanofi Pasteur	France	10 μg§
GenHevac B	Sanofi Pasteur	France	20 μg
Euvax-B	LG Life Sciences Ltd	South Korea	20 μg
Hepavax-Gene	Crucell Korea (Berna Biotch Korea Corp)	South Korea	20 μg
Hepatitis B vaccine (rDNA; Gene Vac-B)	Serum Institute of India Ltd	India	20 μg†
Shanvac-B (Senvac)	Shantha Biotechnics Priviate Ltd	India	20 μg†
Revac-B+	Bharat Biotech International Ltd	India	20 μg
Hepatitis B vaccine recombinant	Bio Farma	Indonesia	20 μg
Heberbiovac HB	Center for Genetic Engineering and Biotechonology	Cuba	20 μg

Brand names may vary by country. This list was compiled from a search of the WHO website for WHO-prequalified hepatitis B vaccines,[40] with the addition of Recombivax HB, Twinrix, GeneHevac B, and HBVAXPRO.

*Recommended dose schedule: 0, 1, and 6 months.

†40 μg at 0, 1, 2, and 6 months for haemodialysis patients.

‡Also contains 720 ELISA units of inactivated hepatitis A virus.

§40 μg at 0, 1, and 6 months for haemodialysis patients (booster at 12 months is recommended for HBVAXPRO if anti-HBs <10 IU/ml at 12 months after first vaccine).

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Table 3

Hepatitis B vaccine efficacy in adults with HIV in the HAART era

	HBV vaccine	Dose*	N†	Study design	Country	Mean/median CD4 cell count (cells per μL)	% on HAART	Median HIV VL copies per ml	% vaccine response	Predictors of vaccine response
Standard dose vaccine										
Rey et al, 2000[30]	GenHevac B	20 μg at 0, 1, 2 months	20	Prospective	France	470 (median; excluded CD4 cell count <200)	85%	3·37 $\log_{10}$	55%	CD4 cell count >500; (HIV VL not assessed)
Tedaldi et al, 2004[15]	Not reported	Not reported	51	Retrospective	USA	584 responders (median), 384 non-responders‡ (median)	71%	Not reported	37·2%	Nadir and median CD4 cell count ≥200; undetectable HIV VL
Overton et al, 2005[31]	Engerix-B	10 μg	194	Retrospective	USA	449 responders (mean), 415 non-responders (mean)	82%	<400 responders, 3·58 $\log_{10}$ non-responders	17·5%	Undetectable HIV VL§
Ungulkraiwit et al, 2007[32]	Engerix-B	20 μg	65	Prospective	Thailand	345 (mean)	88%	<50	46%	Age, mean CD4 cell count
Paitoonpong et al, 2008[33]	Engerix-B	20 μg	28	Prospective	Thailand	324 (mean)	100%	<50	71·4%	Mean CD4 cell count§, HAART regimen with efavirenz§
Kim et al, 2008[34]	Engerix-B or Twinrix	20 μg	97	Retrospective	USA	325 (mean)	31%	Not reported; 24% VL <400	44%	CD4 cell count nadir >200§, undetectable HIV VL§, age <40 years§, not African–American race§
Bailey et al, 2008[35]	Engerix-B or Recombivax HB	20 μg	125	Retrospective	USA	502 responders (median), 346 non-responders (median)	78%	Not reported; 46% VL <400	47·2%	HIV VL§
Landrum 2009[36]	Not reported	Not reported	626	Retrospective	USA	519 (median)	33%	2·90 $\log_{10}$ (at last vaccine)	35%¶	On HAART at last vaccine§, ≥3 vaccines§, female sex§

	HBV vaccine	Dose*	N†	Study design	Country	Mean/median CD4 cell count (cells per μL)	% on HAART	Median HIV VL copies per ml	% vaccine response	Predictors of vaccine response
Pettit 2010[37]	Engerix-B or Twinrix	20 μg	215	Retrospective	USA	420 (mean)	66%	4·72 $\log_{10}$ (mean)	46·5%	CD4§, younger age§, Twinrix vs Engerix (p=0·003)§
de Vries-Sluijs 2011[38]	HBvaxPro	10 μg at 0, 1, 3 weeks *vs* 10 μg at 0, 1, 6 months	761	Randomised non-inferiority	Netherlands	440 (median)	71%	Not reported; 59% with VL <50	38·7% (weekly schedule); 50% (monthly schedule); (Δ=11·3%; 95% CI 4·3–18·3)	CD4 cell count§, HAART use, female sex, undetectable HIV VL, longer duration of HAART
Double-dose vaccine										
Fonseca et al, 2005[79]	Engerix-B	20 μg *vs* 40 μg	192	RCT	Brazil	429 (mean)	86%	2·69 $\log_{10}$	34% standard dose; 47% double dose (p=0·07)	CD4 cell count ≥350§, HIV VL <10 000 copies per mL§
Pasricha et al, 2006[80]	Senvac HB	40 μg	40	Prospective	India	393 (CD4 cell count ≥200; mean), 117 (CD4 cell count <200; mean)	0%	Not reported	100% CD4 cell count ≥200; 47% CD4 cell count <200	CD4 cell count ≥200 in treatment naive patients (HIV VL not assessed)
Cornejo-Juarez et al, 2006[81]	Recombivax HB	10 μg *vs* 40 μg	79	RCT	Mexico	245 (10 μg) (mean), 225 (40 μg) (mean)	65%	4·88 $\log_{10}$ 10 μg; 4·83 $\log_{10}$ 40 μg	62% 10 μg; 60% 40 μg (p=0·9)	CD4 cell count ≥200§
Viega et al, 2006[82]	EUVAX B	40 μg	47	Prospective	Brazil	452 responders (median), 359 non-responders (median)	91%	2·86 $\log_{10}$ responders; 3·63 $\log_{10}$ non-responders	64%	HIV VL§, memory CD4 cells at baseline§
Cruciani et al, 2009[55]	HBVAXPRO	40 μg at 0, 1, 2, months	65	Prospective	Italy	533 (median; excluded CD4 cell count <200)	80%	<100	60%	CD4 count§, HIV VL <1000§, female sex§
Potsch et al, 2010[83]	EUVAX B	40 μg at 0, 1, 2, 6 months	47	Prospective	Brazil	402 (median)	79%	Not reported; 70% with VL <80	89%	Undetectable HIV VL
Launay et al, 2011[84]	GenHevac B	20 μg intramuscularly *vs* 40 μg intramuscularly at 0, 1, 2, 6 months	437	RCT	France	516 (20 μg intramuscularly) (median), 509 (40 μg intramuscularly) (median; excluding CD4 cell count	84%	Not reported; 78% with VL <50	65% 20 μg intramuscularly; 82% 40 μg intramuscularly (p<0·001)	CD4 cell count§, undetectable HIV VL§, younger age§, no active smoking§

	HBV vaccine	Dose*	N†	Study design	Country	Mean/median CD4 cell count (cells per μL)	% on HAART	Median HIV VL copies per ml	% vaccine response	Predictors of vaccine response
						<200)				
Potsch et al, 2012[85]	EUVAX B	40 μg at 0, 1, 2, 6 months	163	Prospective	Brazil	385 (median)	80%	Not reported; 70% with VL <80	83% (3 doses); 91% (4 doses)	Undetectable HIV VL

RCT=randomised controlled trial. VL=viral load. HAART=highly active antiretroviral therapy. HBV=hepatitis B virus.

*Administered at standard schedule of 0, 1, and 6 months, unless reported otherwise.

†Number of participants on whom post-vaccination anti-HBs was done.

‡Nonresponders.

§Predictor on multivariate analysis.

¶% on HAART at time of last vaccination.

Table 4

Repeat HBV vaccination efficacy in adults with HIV who did not respond to primary HBV vaccine series

	HBV vaccine	Previous dose/ schedule	Dose/schedule for repeat vaccination	N*	Study design	Country	Mean/median CD4 cell count (cells per μL)	% on HAART	Median HIV VL copies per ml	% vaccine response after repeat series	Predictors of vaccine response for revaccination
Rey et al, 2000[30]	GenHevac B	20 μg at 0, 1, 2 months	20 μg at 0, 1, 2 months	9	Prospective	France	Not reported for non-responders	Not reported	Not reported	78%	Not assessed
de Vries-Sluijs et al, 2008[87]	HBVAXPRO	10 μg at 0, 1, 6 months	20 μg at 0, 1, 2 months	144	Prospective	Netherlands	360 (median)	67%	Not reported; 62% HIV VL <50	50·7%	Female sex†, age <40†, if age ≥40 years HIV VL <50 copies per mL†
Cruciani et al, 2009[55]	HBVAXPRO	40 μg at 0, 1, 2 months	40 μg at 0, 1, 2 months	26	Prospective	Italy	Not reported for non-responders	Not reported	Not reported	73%	Not assessed
Bloom et al, 2009[88]	Not reported	Not reported	Not reported; 1, 2, or 3 vaccinations after primary series	63	Retrospective	USA	557 (mean) responders, 435 (mean) non-responders‡	75%	Not reported; 67% HIV VL undetectable	29% overall; of those with 3 extra vaccines, 36% responded	No significant predictors on multivariate analysis
Pettit et al, 2010[37]	Engerix-B	Engerix-B or Twinrix 20 μg at 0, 1, 6, months	40 μg at 0, 1, 6 months	30	Retrospective	USA	563 (mean) responders, 306 (mean) non-responders	87%	3·36 $\log_{10}$ responders; 3·96 $\log_{10}$ non-responders	66·7%	CD4 cell count†
Psevdos et al, 2010[89]	Recombivax HB	20 μg at 0, 1, 6 months	Median 3 (range: 1–5) additional doses of 20 μg *vs* median 3 (range: 3–8) additional doses of 40 μg	101	Retrospective	USA	380 (median)	90%	Not reported; 72% HIV VL <400 copies per ml	59% 20 μg dose re-vaccination; 85% 40 μg dose re-vaccination (p=0·006)	Double dose,† CD4 cell count ≥200†, HAART†

HBV=hepatitis B virus. HAART=highly active antiretroviral therapy. VL=viral load.

*Number of nonresponders to standard primary series who received repeat vaccination series and had anti-HBs assessed after repeat vaccination series.

†Predictor on multivariate analysis.

‡Non-responders.

Table 5
Adjuvants used in HBV vaccines that have been assessed in RCTs

	Populations studied	Results from RCT comparing adjuvanted with unadjuvanted HBV vaccine
GM-CSF	Adults with HIV	One study showed higher rates of seroprotection for adjuvanted vaccine;[93] one study showed no improvement in seroprotection for adjuvanted vaccine[94]
CPG 7909	Adults with HIV	Higher rates of seroprotection and higher antibody titres for adjuvanted vaccine[95]
1018 ISS	Healthy adults aged 40–70 years	Higher rates of seroprotection and higher antibody titres for adjuvanted vaccine[96]
AS04	Pre-haemodialysis (creatinine clearance ≤30 mL/min) and haemodialysis patients	Improved rates of seroprotection, higher antibody titres, and greater persistence of seroprotection for adjuvanted vaccine[97]
AS02	Pre-haemodialysis (creatinine clearance ≤30 mL/min), peritoneal dialysis, and haemodialysis patients	Improved rates of seroprotection and higher antibody titres for adjuvanted vaccine[98]

HBV=hepatitis B virus. RCT=randomised controlled trial. GM-CSF=granulocyte-macrophage colony-stimulating factor.