

Hepatitis B and A vaccination in HIV-infected adults: A review

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Hepatitis B and A account for considerable morbidity and mortality worldwide. Immunization is the most effective means of preventing hepatitis B and A. However, the immune response to both hepatitis vaccines seems to be reduced in HIV-infected subjects. The aim of this review was to analyze the immunogenicity, safety, long-term protection and current recommendations of hepatitis B and A vaccination among HIV-infected adults. The factors most frequently associated with a deficient level of anti-HBs or IgG anti-HAV after vaccination are those related to immunosuppression (CD4 level and HIV RNA viral load) and to the frequency of administration and/or the amount of antigenic load per dose. The duration of the response to both HBV and HAV vaccines is associated with suppression of the viral load at vaccination and, in the case of HBV vaccination, with a higher level of antibodies after vaccination. In terms of safety, there is no evidence of more, or different, adverse effects compared with HIV-free individuals. Despite literature-based advice on the administration of alternative schedules, revaccination after the failure of primary vaccination, and the need for periodic re-evaluation of antibody levels, few firm recommendations are found in the leading guidelines.

Introduction

With the advent of effective antiretroviral treatment, life expectancy for people living with the human immunodeficiency virus (HIV) is now approaching that of the general population. Consequently, the relative importance of non-AIDS-related morbidities has increased. After AIDS-related deaths and non-AIDS-

defining cancers, liver disease is the third underlying cause of death in people living with HIV.¹

Viral hepatitis is a major global health issue affecting nearly 400 million people worldwide.² Due to shared modes of transmission, a high proportion of adults at risk for HIV infection are also at risk for hepatitis B virus (HBV) infection. Reciprocal interactions between HIV and HBV lead to an increased risk for severe, life-threatening complications.³ Hepatitis A virus (HAV) infection, mainly transmitted through the faecal-oral route, can cause mild-to-severe illness but does not lead to chronic infection.⁴ HIV-infected people may experience prolonged HAV viremia, which has important public health implications for transmission within the community.⁵ Numerous studies have searched for new strategies to improve response rates after HBV vaccination and improve long-term antibody persistence: higher hepatitis B vaccine doses and/or prolongation of the vaccination schedule, use of the intradermal route, and adding vaccine adjuvant. The immunogenicity of hepatitis A vaccines in HIV-infected adults has also been assessed in several studies.^{6–8}

The objective of this review was to describe the state-of-the art of HBV and HAV vaccination in HIV-infected adults. As part of this update, a comprehensive literature review of seroprotection rates and factors associated with the immunogenicity to HBV and HAV vaccination in HIV-infected adults in the highly active antiretroviral therapy (HAART) era was made. This new review updates that published on the same topic in 2012:⁸ the results of studies published until 2015, including both clinical trials and all observational studies that complied with the selection criteria of the search strategy used, have been included (Fig. 1).

HBV Vaccination in HIV-Infected Subjects

HBV/HIV co-infection: epidemiology and natural history

The introduction of effective vaccination programs in many countries has resulted in a significant decrease in the incidence of HBV infection, although it remains an important cause of morbidity and mortality worldwide.⁹ The predominant mode of transmission of HBV varies between different geographical areas. Perinatal infection is the predominant mode of transmission in areas of high prevalence, horizontal transmission, particularly in early childhood, accounts for most cases of chronic HBV infection in areas of intermediate prevalence, while unprotected sexual

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We used the search terms “Hepatitis B” or “HBV”, “Hepatitis A” or “HAV”, combined with “Vaccine” or “Vaccination” and “HIV”. In the analysis of immunogenicity levels and factors associated to HBV and HAV vaccination (*table 1 and 2*), only original studies (with sample sizes ≥ 40 subjects) in HIV-infected adults in the HAART era were finally included (n=23 for studies on hepatitis B vaccination and n=13 on hepatitis A vaccination). *Appendix 1 and 2* show the flow chart for the search with the complete panel of inclusion and exclusion criteria for studies assessing the immunological response following hepatitis B and A vaccination. For the review of safety, the duration of seroprotection and vaccination coverages in HIV-infected subjects, other relevant articles were identified after screening reference lists of articles retrieved by the above mentioned search strategy and the authors’ personal archives.

Figure 1. Search strategy and selection criteria of articles included in the review.

intercourse and intravenous drug use in adults are the major transmission routes in areas of low prevalence.¹⁰

HIV infection shares the above-mentioned routes of transmission, but is about 100-times less infectious. Consequently, in some settings, up to 2 thirds of all HIV-infected people have a blood marker of past or present HBV infection.^{11,12} With a global prevalence of coinfection of around 10%, among HIV-infected individuals, estimates of chronic HBV infection in HIV-infected subjects are much lower in western countries, but are still remarkable, being up to 20-times higher than in the general population.¹³⁻¹⁵ In areas of low endemicity, such as North America, Australia and Western Europe, the prevalence of chronic coinfection is around 5–7% in HIV-infected individuals.¹⁵ In countries with intermediate and high HBV endemicity, coinfection rates range from 10 to 20%.¹⁶⁻¹⁸

HIV appears to be a risk factor for the reactivation of HBV infection in patients who have developed HBV surface antibodies, especially those with severe immunodeficiency.^{11,19} Although, the degree of HIV-induced immunosuppression does not seem to correlate well with liver injury,²⁰ a higher risk of chronicity after acute HBV infection has been shown²¹ as have increased carriage rates and greater viral replication.^{20,22,23} Higher levels of HBV replication not only increase the risk of HBV transmission but also result in more-rapid progression of liver fibrosis, with a higher risk of cirrhosis and end-stage liver disease, especially in patients with low CD4+ cell nadir counts.¹²

Conversely, there is less evidence on the effects of HBV on the natural history of HIV progression.²⁴ Prospective studies have shown an increased risk of progression to AIDS in patients with HBV coinfection.^{25,26} It also seems that lower CD4+ cell counts may increase the risk for hepatocellular carcinoma (HCC) in people living with HIV, an effect that was particularly evident for HBV-related HCC in non-injecting drug users in the case-control study by Clifford et al.²⁷

Hepatitis B vaccines for adults

The first recombinant HBV vaccine was introduced in 1986 and has gradually replaced the plasma-derived HBV vaccines that became commercially available in 1982. The recombinant vaccine contains more than 95% HBsAg protein (5 to 40 $\mu\text{g}/\text{mL}$); yeast-derived proteins may constitute up to 5% of the final product but no yeast DNA is detectable in the vaccine. Vaccine HBsAg is adsorbed to aluminum hydroxide or aluminum phosphate.^{28,29} Currently-available US. Food and Drug Administration (FDA)-approved HBV vaccines for adults include: Engerix-B (GlaxoSmithKline, Belgium), containing 20 μg HBsAg; Recombivax HB (Merck, USA) containing 10 μg HBsAg; and the combined HAV + HBV Twinrix (GlaxoSmithKline, Belgium), containing 20 μg HBsAg and 720 ELISA units of inactivated HAV.³⁰ The European Medicines Agencies (EMA) only shares with the FDA the approval of Twinrix. The two non-combined HBV vaccines approved by the EMA that differ from those approved by the FDA are: HBVax-PRO (Sanofi Pasteur MSD, Lyon) containing 10 or 40 μg HBsAg (for use only in predialysis and dialysis patients aged ≥ 18 years), and Fendrix (GlaxoSmithKline, Belgium), containing 20 μg HBsAg and adjuvanted by AS043, which is only indicated in patients with kidney disease.³¹ Currently, there are no specific hepatitis vaccines or special indications for immunocompromised subjects with HIV in the summary of product characteristics of the licensed hepatitis vaccines.

Hepatitis B vaccines: efficacy and safety

The protective efficacy of HBV vaccination is related to the induction of anti-HBs antibodies, but also involves the induction of memory T-cells. An anti-HBs concentration of ≥ 10 IU/L measured 1–3 months after administration of the last dose of the primary vaccination series is considered a reliable marker of protection against infection.^{28,32} The primary 3-dose vaccine series induces protective antibody concentrations in $>95\%$ of healthy children, adolescents and adults.^{28,33-35} The protection provided by 3 or 4 doses of monovalent HB vaccine persists for at least 2 decades in the great majority of immunocompetent individuals.³⁶ The HBV vaccine is well-tolerated by newborns, children and adults, with injection site pain being the most common reported adverse event.³⁷⁻⁴¹ The WHO Global Advisory Committee on Vaccine Safety (GACVS) has endorsed the excellent safety profile of the HBV vaccine.²⁸

Immunological response after HBV vaccination in HIV-infected adults: associated factors

A diminished response to HBV vaccination among immunocompromised adults has repeatedly been shown.⁴²⁻⁴⁴ This

Table 1. Studies assessing the immunological response after HBV vaccination in adults in the HAART era

Author / Year	Study design	Vaccine manufacturer and schedule	Baseline immunological status of participants	Response rate (%) [*]	Main findings [#]
Sasaki Md et al. ⁵⁸ 2003	RCT	Engerix-B, (a) 40 µg at 0,1,6 months vs. (b) 40 µg at 0,1,6 months plus 20 µg th GM-CSF at first visit	(a) CD4 count median=462 cells/mm ³ (b) CD4 count median=487 cells/mm ³	(a) 60.0% (24/40) (b) 72.5% (29/40)	GM-CSF increases the immunogenicity of recombinant HBV vaccine
Fonseca et al. ⁴⁶ 2005	RCT	Engerix-B, (a) 20 µg at 0,1,6 months vs. (b) 40 µg at 0,1,6 months	(a+b) 90% on HAART CD4 count mean=429 cells/mm ³ 86% on HAART	Overall: 40.6% (78/192) (a) 34.0% (32/94) (b) 46.9% (46/98)	Protective antibody response was associated with 40µg dose compared with the standard dose for patients with CD4 cell counts ≥ 350 cells/mm ³ . 40 µg-schedule also improved seroconversion compared with standard dose for patients with HIV viral load <10,000 copies/mL A plasma HIV RNA level of <400 copies/mL was associated with a protective antibody response
Overton et al. ⁵⁵ 2005	Retrospective	Engerix-B, 10 µg at 0,1,6 months	Responders: CD4 count mean=449 cells/mm ³ at baseline 85% on HAART Non-responders: CD4 count mean=415 cells/mm ³ at baseline 82% on HAART	17.5% (34/194)	
Cornejo-Juarez et al. ⁵⁷ 2006	RCT	Recombivax HB, (a) 10 µg at 0,1,6 months vs. (b) 40 µg at 0,1,6 months	(a) CD4 count mean = 245 cells/mm ³ (b) CD4 count mean = 225 cells/mm ³	(a) 61.5% (24/39) (b) 60.0% (29/40)	Protective antibody response was associated with being female and having a higher CD4 count
Veiga et al. ⁵⁹ 2006	Prospective observational	EUVAX B, 40 µg at 0,1,6 months	(a+b) 65% on HAART Responders: CD4 count median = 452 cells/mm ³ at baseline Non-responders: CD4 count median = 359 cells/mm ³ at baseline	63.8% (30/47)	Protective antibody response was associated with higher CD4 count and lower plasma HIV RNA
Ungulkruiwit et al. ⁴⁷ 2007	Prospective observational	Engerix-B, 20 µg at 0,1,6 months	CD4 count mean = 345 cells/mm ³ 91% on HAART 88% on HAART	46.2% (30/65)	Protective antibody response was associated with younger age and higher CD4 cell count
de Vries-Sluijs et al. ⁶⁷ 2008	Prospective observational	HBVAXPRO, 10 µg at 0,1,2 months Re-vac: 20 µg, at 0,1,2 months	CD4 count median = 360 cells/mm ³ 67% on HAART	Overall (after one or 2 series): 50.7% (73/144)	Protective antibody response was associated with female sex. For patients with a detectable HIV RNA load, serological response at revaccination was lower in those ≥ in those ts w
Kim et al. ⁴⁸ 2008	Retrospective	Twinrix or Engerix-B, 20 µg at 0,1,6 months	CD4 count mean = 325 cells/mm ³ 31% on HAART	44.3% (43/97)	Protective antibody response was associated with age < 40 years, not alcohol abuse, CD4 nadir > 200, HIV RNA < 400 copies/ml and not African-American race

Bailey et al. ⁴⁹ 2008	Retrospective	Engerix-B or Recombivax HB, 20 µg at 0,1,6 months	Responders: CD4 count median = 502 cells/mm ³ at baseline 81% on HAART Non-responders: CD4 count median = 346 cells/mm ³ at baseline 74% on HAART	CD4 count median = 47.2% (59/125)	Protective antibody response was associated with HIV RNA < 10,000 copies/ml
Cruciani et al. ⁶⁶ 2009	Prospective observational	HBVAXPRO, 40 µg at 0,1,2 months Re-vac: 1 to 3 doses	CD4 count median = 533 cells/mm ³ (excluding CD4 count < 200) 80% on HAART	Overall: 89.2% (58/65) After primary schedule: 60.0% (39/65) Re-vac: 1 to 3 doses: 73.1% (19/26) After one year, 70.6% (41/58) and after 2 years, 32.7% (19/58) had persistence of anti-HBs	Protective antibody response was associated with female sex, higher CD4 count, and HIV viral load < 1,000 copies. Anti-HBs titres after 1–3 booster dose/s significantly lower in non-responders than in responders to primary vaccination. Persistence of anti-HBs may be related to antibody titres after immunization.
Potsch et al. ⁶⁰ 2010	Prospective observational	EUVA B, 40 µg at 0,1,2,6 months	CD4 count median = 402 cells/mm ³ 79% on HAART	89% (42/47)	Protective antibody response was associated with undetectable HIV RNA load.
Psevdos et al. ⁵⁰ 2010	Retrospective	Recombivax HB, 20 µg, at 0,1,6 months. Re-vac: 1 to 5 additional doses of 20 µg or with 3 to 8 additional doses of 40 µg	CD4 count median = 380 cells/mm ³ 90% on HAART	After primary schedule: 34.7% (126/363) Re-vac: after additional 20 µg dose/s: 59.0% (36/61); after additional 40 µg doses: 85.0% (34/40)	Protective antibody response at re-vaccination was associated with HAART use and CD4 cell counts ≥ 200 cells/mm ³ , as was 40 µg HBV revaccination dosage
Overton et al. ⁶³ 2010	RCT	Recombivax HB, (a) 40 µg at 0,1,3 months vs. (b) 40 µg plus 250 µg GM-CSF at 0,1,3 months	CD4 count median = 446 cells/mm ³ 77% on HAART	Overall: 59.1% (26/44) (a) 65.2% (15/23) (b) 52.4% (11/21)	GM-CSF as an adjuvant did not improve the anti-HBs titres or the development of protective immunity. Subjects who developed immunity were significantly younger than those who did not
Pettit et al. ⁵¹ 2010	Retrospective	Engerix-B or Twinrix, 20 µg at 0,1,6 months Re-vac: Engerix-B 40 µg at 0,1,6 months	CD4 count mean = 420 cells/mm ³ 66% on HAART	After primary schedule: 46.5% (100/215) Re-vac: 66.7% (20/30)	Protective antibody response associated after primary schedule with younger age, higher CD4 count and receipt of Twinrix vs. Engerix-B.
Overton et al. ¹³⁰ 2011	RCT	One booster dose in previous non-responders: Recombivax HB, (a) 40 µg vs. (b) 40 µg plus 250 µg GM-CSF	(a) CD4 count median = 375 cells/mm ³ (b) CD4 count median = 425	Overall: 42% (24/57) (a) 50.0% (14/28) (b) 34.5% (10/29)	GM-CSF failed to improve responses to the booster HBV vaccination

(Continued on next page)

Table 1. Studies assessing the immunological response after HBV vaccination in adults in the HAART era (*Continued*)

Author / Year	Study design	Vaccine manufacturer and schedule	Baseline immunological status of participants	Response rate (%) ^a	Main findings [#]
de Vries-Sluijs et al. ⁵⁶ 2011	Randomized non-inferiority trial	HBVAXPRO, (a) 10 µg at 0,1,3 weeks vs. at (b) 10 µg at 0,1,6 months	cells/mm ³ 70% on HAART CD4 count median = 440 cells/mm ³ 71% on HAART	(a) 38.7% (142/367) (b) 50.0% (197/394)	The efficacy of an accelerated schedule was non-inferior in those with CD4 cell count > 500 cells/mm ³
Launay et al. ⁵² 2011	RCT	(a) GenHevac B, 20 µg i.m at 0,1,6 months vs. (b) 40 µg i.m at 0,1,2,6 months vs (c) 4 µg i.d at 0,1,2,6 months	CD4 count median = (a) 516, (b) 509, (c) 482 cells/mm ³ (a) 86%, (b) 80%, (c) 86% on HAART	(a) 64.5% (91/141) (b) 82.1% (119/145) (c) 77.1% (108/140)	Both the 4 intramuscular double-dose regimen and the 4 intradermal low-dose regimen improved serological response compared with the standard HBV vaccine regimen. Protective antibody response was associated with higher CD4 count, undetectable HIV RAN viral load, younger age and no smoking
Kim et al. ⁶⁵ 2012	Retrospective	Non-responders after a standard schedule: Re-vac: Recombivax HB, 40 µg at 0,1,2 months	CD4 count median = 433 cells/mm ³ 91% on HAART	Re-vac: 81.5% (44/54) 57.6% (19/33) had persistent protective anti-HBs titres 12 months later	Protective anti-HB titres may decrease over time after successful 40 µg HBV rescue vaccination in HIV-infected patients. HIV viral load suppression could improve the persistence of anti-HB titres.
Mena et al. ⁶² 2012	Retrospective	Engerix-B, HBVAXPRO or Twinrix, 20 or 40 µg at (a) 0,1,6 months vs. (b) 0,1,2 months vs. (c) 0,7,14–21 d Re-vac schedules also included.	CD4 count median = 488 cells/mm ³ 62% on HAART	Overall: 60.3% (286/474) (a) 69.2% (157/235) (b) 58.1% (93/160) (c) 50.0% (14/28)	Protective antibody response was associated with lower HIV RNA viral load and CD4 count ≥ 350 cells. Patients receiving less than 3 doses of vaccine or 3 doses of the rapidly accelerated schedule had a lower probability of response in comparison with those receiving 3 doses of an accelerated schedule
Potsch et al. ⁶¹ 2012	Retrospective	EUVAX B, 40 µg at 0,1,2,6 months	CD4 count median = 385 cells/mm ³ 80% on HAART	After the third dose: 83.4% (136/163) After the fourth dose: 90.8% (148/163)	Strong protective antibody response was associated with undetectable HIV-1 viral load and higher CD4 count after 4 doses. Patients with undetectable HIV viral load were almost 3 times more likely to have anti-HBs titres above 100 mIU/mL than those with detectable viral load

Chaiklang et al. ⁵³ 2013	RCT	Hepavax-Gene, (a) 20 µg at 0,1,6 months vs. (b) 20 µg at 0,1,2,6 months vs. (c) 40 µg at 0,1,2,6 months	CD4 count median = (a) 400, (b,c) 544 cells/mm ³ 100% on HAART	(a) 86.6% (39/44) (b) 93.2% (41/44) (c) 95.5% (42/44)	The standard 3 dose HBV vaccination in HIV infected adults with CD4+ cell counts > 200 cells/mm ³ and undetectable plasma HIV-1 RNA is highly effective. Although regimens of 4 injections of either standard or double doses could not significantly increase the response rate, these regimens may induce higher levels of virus antibodies
Irungu et al. ⁶⁴ 2013	Prospective observational	EUVAX-B, REVACC-B or SHANVAC-B at 0,1 to 3, and 6 months. Re-vac: 0,1,6 months.	557 cells/µL 0% on HAART (5 participants initiated HAART during the study period)	After the third dose: 64,2% (199/310) Re-vac: 83,3% (88/102)	Protective antibody response to initial vaccination was associated with higher CD4 count and female sex. Higher body mass index, lower plasma HIV-1 RNA levels, and shorter time to revaccination predicted protective response to re-vaccination
Rock et al. ⁵⁴ 2013	Retrospective	Engerix-B 20 µg at 0,1,6 months. Re-vac: 40 µg at 0,1,6 months	Responders to a primary schedule: CD4 count mean = 544 cells/mm ³ 56% on HAART Non-responders to a primary schedule: CD4 count mean = 430 cells/mm ³ 51% on HAART	47,3% (147/226) Re-vac: 70%(48/69)	Protective antibody response to initial vaccination was associated with higher absolute numbers and percentages of CD4 cells and responders were more likely to be receiving HAART

¹Inclusion and exclusion criteria: Appendix 1.

*Protective titre: Anti-HBs ≥ 10 UI/L.

#Associated factors in a multivariate analysis / Factors at baseline.

-RCT: Randomized Controlled Trial. RDBCT: Randomized Double-Blind Controlled Trial. GMT: Geometric Mean Titre. HAART: Highly active antiretroviral therapy. GM-CSF: Granulocyte Macrophage Colony-Stimulating Factor.

includes HIV-infected subjects.⁴⁵ As shown in Table 1, the immune response to a 20 µg HBsAg dose embedded within the standard schedule of HBV vaccination (0, 1 and 6 months) in HIV-infected adults is suboptimal, ranging from 34.0% to 88.6%.⁴⁶⁻⁵⁴ Of the 9 studies evaluating the response after 3 doses of 20 µg HBsAg that were included in our review, the results of the 3 randomized clinical trials (RCT) included (all with >80% subjects on HAART) showed wide disparities (34.0% to 88.6%).^{46,52,53} Observational studies assessing the effects of 3 doses of 20 µg HBsAg found seroconversion rates of between 34.7 and 47.2% after vaccination.⁴⁷⁻⁵¹ The same schedule of 3 doses, but using 10 µg HBsAg, was evaluated in a retrospective study with a very-high proportion of subjects on HAART which found a seroconversion rate of only 17.5%,⁵⁵ the worst reported until now. Half of the patients included in the non-inferiority RCT by de Vries Sluijs et al., after receiving either one (10 µg) or 2 (10 µg and 20 µg) series at 0,1 and 2 months,⁵⁶ and 61.5% of those in the RCT by Cornejo-Juarez et al.,⁵⁷ responded to 3 doses of 10 µg HBsAg. These studies used 10 µg of *HBvax-Pro*, which is equivalent to 20 µg of *Engerix B*.

Four prospective studies evaluated the 0, 1 and 6 months schedule with 40 µg HBsAg per HBV vaccine shot.^{46,57-59} The proportion of subjects who seroconverted ranged between 46.9% in the RCT by Fonseca et al.⁴⁶ and 63.8% in the observational study by Veiga et al.⁵⁹ Four other studies evaluated the immunogenicity after 4 vaccine doses at 0, 1, 2 and 6 months (accelerated schedule);^{52,53,60,61} a protective antibody response was observed in 89.4% and 90.8% of subjects receiving 4 doses of 40 µg in 2 observational studies.^{60,61} The RCT by Launay et al. also showed that both the 4 40 µg-intramuscular and the 4 4 µg-intradermal schedules improved the serological response (82.1% and 77.1%, respectively), compared with the standard 20 µg-intramuscular HBV vaccine schedule (64.5%).⁵² The fourth and most recent study, a RCT, found no statistically significant differences in the proportion of responders between the standard schedule (88.6%) and 20 or 40 µg HBsAg in a 4 dose-schedule (93.2% and 95.5%, respectively).⁵³ Finally, 3 doses of a rapidly-accelerated schedule at 0, 1, and 2–3 weeks were evaluated in one RCT, and found that 38.7% of subjects developed seroprotection with the 10µg dose of *HBVaxPro*,⁵⁶ while a retrospective study using 20µg of HBsAg found a seroprotection rate of 50%.⁶²

Two of the studies included in our review evaluated the use of adjuvants as stimulators of immunogenicity of the vaccine. Twenty µg of recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) was administered concomitantly with the first vaccine dose of 40 µg HBsAg, increasing the immunogenicity of the recombinant HBV vaccine (72.5% vs. 60% in controls) after a 3-dose schedule.⁵⁸ Conversely, a more-recent RCT did not confirm greater protective immunity in patients receiving 250 µg GM-CSF as an adjuvant to a 40 µg-accelerated schedule at 0, 1 and 3 months (52.4% vs. 65.2% in controls).⁶³

Studies have also evaluated the immune response of a second schedule after the failure of a primary series of at least 3 doses of HBV vaccine. A 20µg HBV rescue vaccination at 0, 1 and 6 months after the primary series with 3 20µg HBsAg doses at 0,

1 to 3 and 6 months was evaluated in a prospective observational study, and achieved a seroconversion rate of 83.3% in patients completing the 2 schedules.⁶⁴ Two retrospective studies evaluated the response in subjects receiving 40µg HBsAg rescue vaccination at 0, 1, and 6 mo after failure with primary vaccination with the same schedule. They found similar protection rates (66.7% and 70%) in subjects vaccinated with 6 doses.^{51,54} Another retrospective study found a better outcome, with a 81.5% of subjects receiving a rescue schedule of 40µg at 0, 1 and 2 months after failure with a primary standard schedule at 20µg per dose.⁶⁵

The administration of 4 vaccine doses at 0, 1, 2 and 6 months (accelerated schedule), whether of 20 or 40 µg, generally confers a better response to the vaccine. Rescue vaccination with one or more doses also seems to be effective in raising the rate of responders in vaccinate HIV subjects. Intradermal administration and the use of the GM-CSF adjuvant have been associated with the level of seroprotection after vaccination, although the evidence remains poor. There is also insufficient evidence on the administration of ultra-rapid schedules to consider this strategy as an acceptable option in HIV-infected individuals.

Undetectable or minimum HIV RNA viral load and a higher CD4+ cell count at baseline are the factors most-frequently associated with a successful response to HBV vaccination in both RCT and observational studies.^{47-55,57,59-62,64,66} The CD4+ cell count cutoffs most-frequently associated with a better response were >400, >300 and >200 cells/mm.³ Given that the populations analyzed in the studies were widely treated with HAART, and that the combination of antiretroviral drugs can maintain viral loads at low levels for long periods, patient treatment, for which associations were rarely found in multivariate analyses should play an important role in the response to HBV vaccination through HIV RNA viral suppression.^{50,54} Female sex^{57,64,66,67} and younger age^{47,48,51,52} were also repeatedly found to be independent factors for vaccine responsiveness. African-American ethnicity,⁴⁸ alcohol abuse,⁴⁸ and tobacco smoking,⁵² have occasionally been associated with a lack of response.

The response to vaccination may be related as much to direct dysfunction of the memory B cells as to indirect dysfunction due to activation of regulatory T cells and the consequent apoptosis of B cells, which is more frequent in persons immunocompromised due to HIV.⁶⁸⁻⁷⁰ Seroprotective antibody formation after vaccination is reduced with increasing age, when the immune state is more affected. With age, the naïve T cell pool is reduced, because, on encountering their cognate antigen, naïve T cells are primed, acquire a memory phenotype and ultimately die by apoptosis. This physiologic loss of T cells is slow because bursts of immune activation are relieved with periods of relative rest. In HIV infection, an identical process occurs but at a faster pace because of the continuous attendance of pathogens.⁷¹

The main factors associated with the individual lack of response are those related to immunological deterioration. The relationship between the lack of response and sex remains unclear.

Long-term persistence of protective levels of anti-HBs

The duration of protection induced by the hepatitis B vaccine in immunocompetent individuals is not widely understood. Anti-HBs titres decrease over time and can fall below protective concentrations. In HIV-infected subjects this process goes faster.⁷ Few studies have assessed the persistence of anti-HBs ≥ 1 year after the last shot in HIV infected adults. In a prospective study, 65 HIV-infected patients received 40 μg HBsAg at 0, 1, and 2 months.⁶⁶ In non-responders to the initial immunization, 1–3 boosters were administered. The response rate was 60% after primary vaccination and 89.2% after boosters, with antibody titres significantly lower in non-responders than in responders to primary vaccination. However, 12 and 24 months after the last vaccination, only 70.6% and 32.7% of responders, respectively, had persistence of protective anti-HBs titres (≥ 10 IU/L). Persistence of anti-HBs titres was significantly-associated with antibody titres after immunization. A retrospective chart review by Kim et al. included HIV-infected patients who received the 40 μg HBsAg rescue vaccination at 0, 1, and 2-month intervals after failure with the conventional HBV vaccination series.⁶⁵ Of 54 HIV-infected patients who received the rescue vaccination schedule, 44 (81.5%) achieved protective anti-HB titres. Of the 33 patients whose anti-HB titres were evaluated 12 months later, 19 (57.6%) had persistent protective anti-HB titres. An undetectable HIV viral load at baseline and follow-up was associated with the presence of protective antibody rates.

Results of 2 observational studies assessing the long-term response to hepatitis B vaccination are of interest. In one study, after a median follow-up of 43 months, 111 of the 152 participants (73%) maintained protective levels of anti-HBs. In this case, HIV RNA suppression at vaccination was also associated with persistence of protective levels of anti-HBs.⁷² In a 5-year prospective study by Lopes et al.,⁷³ the durability of an effective anti-HBs level appeared to be significantly-associated with a higher level of antibody titres after primary immunization. The mean time to loss of effective anti-HBs titres was 2.0, 3.7 and 4.4 y for patients with anti-HBs titres of 10–100 IU/L, >100–1000 IU/L and >1000 IU/L respectively at primary vaccination. Sixty-eight of the 155 initial responders (43.9%) maintained seroprotection rates at the last determination.

B-cell dysfunction in HIV, which is more frequent in patients with detectable viral loads and low levels of CD4+ lymphocytes, is also related to the loss of memory and undetectable levels of anti-HBs over time.⁷⁴

Safety of HBV vaccination in HIV-infected adults

HBV vaccination of HIV-infected and non-HIV infected subjects shows a similar safety profile. A recent RCT using 20 μg HBsAg in an accelerated or standard schedule, or 40 μg in an accelerated schedule found that the most-common adverse events were pain at the injection site (42.4%), fatigue (10.6%) and swelling at the injection site (10.1%). Pain at the injection site was significantly-more common in the 40 μg group. There were no serious adverse events (SAEs) related to any vaccination schedule.⁵³

One RCT⁵² compared the safety and immunogenicity of 4 intramuscular 40 μg dose and 4 intradermal 4 μg regimens vs. the standard intramuscular 20 μg HBV vaccine regimen. This study found the most common adverse events were very similar to those found by the previously-mentioned study. Patients in the intramuscular (i.m.) 40 \times 4 group experienced a higher rate of fever, nausea, and edema, and patients in the intradermal (i.d.) 40 \times 4 group experienced a higher proportion of local adverse reactions (except pain, which was less frequent) than patients in the i.m. 20 \times 3 group. Only one serious adverse event (severe cytotoxicity) possibly related to the vaccine was reported in the i.m. 40 \times 4 group. A higher incidence of injection site adverse events was reported in the i.d. 40 \times 4 group compared with the i.m. 20 \times 3 group. The proportion of solicited systemic reactions was generally similar between the 3 groups. However, the RCT by Fonseca et al.⁴⁶ found more reported adverse events in the 40 μg HBsAg- than in the 20 μg HBsAg-group (both administered at 0, 1 and 6 months). In this case, the most common adverse events were pain at the injection site, headache and fever.

HBV vaccination coverage in HIV-infected population

Coverage of hepatitis B vaccination depends on the degree of implementation of international guidelines, scientific societies and expert panels recommendations used by the different

Table 2. Key issues in hepatitis B vaccination in adults living with HIV

- Viral hepatitis-related liver failure remains the most common main specific cause of liver-related deaths in people living with HIV.
- Reciprocal interactions between HIV and HBV leads to an increased risk for serious, life-threatening complications.
- Higher levels of HBV replication not only increase the risk of HBV transmission but also result in faster progression of liver fibrosis, with a higher risk of cirrhosis and end-stage liver disease, especially in patients with low CD4+ cell nadir counts.
- A diminished response to HBV vaccination in immunocompromised adults has been repeatedly shown. This includes HIV-infected subjects.
- Undetectable or minimum HIV RNA viral load and higher CD4+ cell count at baseline are the factors most-frequently associated with a successful response to HBV vaccination in both RCT and observational studies.
- Younger age and female sex were also repeatedly found to be independent factors for HBV vaccine responsiveness in HIV-infected subjects.
- A higher number of shots and HBsAg dosage have also been shown to play a significant role in anti-HBs seroconversion in HIV-infected patients.
- HIV RNA suppression at vaccination has been associated with the persistence of protective levels of anti-HBs.
- HBV vaccination of HIV-infected and non-HIV infected subjects shows a similar safety profile.
- The BHIVA and the US Guidelines for prevention and treatment of opportunistic infections in HIV-Infected adults and adolescents maintain the need for annual serological testing in immunocompromised individuals who have previously responded after one or 2 series of vaccination.
- Primary vaccination with alternative frequencies of administration, a higher number of doses, a higher concentration of HBsAg per dose, and different routes of administration have not been recommended by any of the guidelines or institutions mentioned in this review.

Table 3. Key issues in hepatitis A vaccination in adults living with HIV

- After infection, the HAV load is higher, the duration of viremia is longer and faecal excretion is prolonged in the case of concurrent HIV infection.
- The immune response to HAV vaccination is reduced in immunocompromised patients, with seroconversion rates ranging from 48.5% to 93.9%.
- Higher CD4 counts are associated with a better vaccine response. Likewise, low HIV RNA viral loads lead to better vaccine response in HIV-infected adults.
- Male sex and HCV co-infection were found to be independent factors for HBV vaccine non-responsiveness in HIV-infected subjects.
- Studies comparing the vaccine response according to whether recipients received 2 or 3 doses of inactivated HAV vaccine found that both the proportion of responders and the GMT of HAV antibodies were higher after the third dose.
- The duration of protection has been associated with suppressed HIV RNA levels at time of vaccination.
- No serious adverse events are usually reported after HAV vaccination regardless of the number of doses or the immunological status, and vaccination has no effect on the course of HIV infection.
- The CDC and WHO recommend vaccinating these subjects if any other medical, behavioral, epidemiological or occupational condition is added to HIV infection. The EACS recommends periodic controls of antibody titres in vaccinated immunocompromised subjects.
- The EACS recommends periodic controls of antibody titres in vaccinated immunocompromised subjects.

countries. A cross-sectional study was performed in HIV-infected patients included in a hospital-based cohort in France in 2011: 2,467 patients were included, with a vaccination coverage of 61.9%.⁷⁵ Factors independently associated with vaccination were a younger age, male sex, men who have sex with men (MSM), and follow-up by an experienced physician. In an observational cohort of over 37,000 HIV-positive individuals attending some of the largest HIV treatment centers in the UK, seroprotection rates increased from 42.0% in 1996 to 58.2% in 2009⁷⁶. An improvement in vaccine coverage and vaccine response rates (as the mean CD4 count of the cohort increased) could both be related to this increase in the seroprotected population. A very-similar overall HBV vaccination coverage was found in a recent cross-sectional study (57.4%) in southern Brazil.⁷⁷ The coverage was lower than that previously reported among HIV-infected adults (76.9%)⁷⁸ in southern Brazil. In the mentioned study, significant inequalities in coverage rates and antibody reactivity in favor of patients with better economic status led the authors to highlight the need for the development of public strategies in order to increase the availability of healthcare services for poorer people.

Among HIV infected adults, given a poorer response rate, prevalence of seroprotection might not be a good proxy for vaccination coverage. In the absence of vaccination data, authors of the UK and Brazilian studies couldn't be certain whether the number of people presenting anti-HBs <10 UI/L was due to failure to vaccinate or to an impaired immune vaccine response in HIV-positive individuals. Lacking other studies on hepatitis B vaccination coverages in HIV-infected subjects, it may be said that, in the studies carried out in UK, France and southern Brazil, around 40% of those not already infected remained at risk of HBV infection at the time of the test result.

Current recommendations on hepatitis B vaccination for HIV-infected patients

The default international recommendation remains the administration of 3 doses of 20 µg HBsAg at 0, 1 and 6 months. The US Guidelines for prevention and treatment of opportunistic infections in HIV-Infected adults and adolescents (Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America),⁷⁹ and the British HIV Association (BHIVA) Guidelines for the Immunisation of HIV-infected Adults⁸⁰ both

recommend serologic determination of antibodies one month and 6–8 weeks, respectively, after administration of the last dose of vaccine. When concentrations of anti-HBs of 10 IU/L are not reached after primary vaccination, revaccination may be considered, according to the CDC's Pinkbook statements.²⁹ The US and the European AIDS Clinical Society (EACS) Guidelines also recommend considering revaccination after primary-schedule vaccination failure.^{79,81} The BHIVA Guidelines go further, recommending rescue vaccination with 3 40 µg doses, given at monthly intervals.⁸⁰

In immunocompetent individuals, long-term persistence of protective levels of anti-HBs after vaccination is variable, and factors related to the loss of seroprotection are currently under study.³⁶ In HIV-infected subjects, loss of memory B cells affects the maintenance of long-term protective titres. In the absence of indications from the CDC, the WHO, and EACS Guidelines, when faced with anti-HBs titres falling below the protective level (10 IU/L), the BHIVA Guidelines maintain the need for annual serological testing in immunocompromised individuals who have previously responded after one or 2 series of vaccination.⁸⁰ The US Guidelines for prevention and treatment of opportunistic infections in HIV-Infected adults and adolescents also suggest yearly assessment for patients with an ongoing risk for HBV acquisition.⁷⁹

Primary vaccination with a higher number of doses or a higher concentration of HBsAg per dose has not been recommended by any of the previously-mentioned institutions or associations.

Hepatitis A Vaccination in HIV-Infected Subjects

HAV/HIV co-infection: epidemiology and natural history

HAV is the most common form of acute viral hepatitis worldwide.⁸² Approximately 1.4 million clinical cases and tens of millions of HAV infections occur every year, although the number of infections is probably much higher due to the high percentage of asymptomatic cases.⁸² HAV is mainly transmitted by the faecal-oral route and its incidence is related to hygiene and access to safe water.⁸³ Clinical hepatitis is more frequent in areas of low or intermediate endemicity (low income countries) and universal vaccination programs against HAV are only recommended in these countries.^{82,83} The prevalence of anti-HAV increases gradually with age, primarily reflecting declining incidence, changing

endemism and, as a result, a lower childhood infection rate over time.⁸⁴⁻⁸⁷ The estimated case-fatality rate ranges from 0.1% in children aged <15 y to 2.1% in adults aged > 40 y.⁸⁸

As the route of infection is faecal-oral, unlike HBV and HIV, it has been postulated that HAV susceptibility among HIV-infected subjects should be similar to that of the general population⁸⁹ and thus HIV infection *per se* would not be a risk factor for HAV infection. However HIV-infected subjects usually experience severe, prolonged courses of infectious diseases due to their impaired immune system: after infection, the HAV load is higher, the duration of viremia is longer and faecal excretion is prolonged in the case of concurrent HIV infection. Thus, HIV-infected subjects are more infectious and for a longer period than non-HIV infected populations.⁵ The normalization of alanine aminotransferase (ALT) levels may also be prolonged in these patients.⁹⁰ Moreover, chronic hepatitis C infection is more frequent among HIV-infected subjects, and this pre-existing hepatic infection could be linked to fulminant acute HAV.⁹¹

Hepatitis A vaccines for adults

The HAV vaccine is the most important preventive strategy against HAV. The HAV vaccine first became available in Europe in 1992 and in the United States in 1995.^{92,93} There are currently 2 types of HAV vaccines: live attenuated and formaldehyde inactivated vaccines. The latter are the most widely used worldwide and are the only ones recommended for HIV-infected subjects. There are several HAV vaccines currently available. Most are adjuvanted with aluminum hydroxide and there are presentations combined with other vaccines (mainly with HBV and typhoid fever).⁹⁴ In the United States, 3 inactivated HAV vaccines are approved by the FDA for adults: 2 single-antigen vaccines: Havrix 1440[®] (manufactured by GlaxoSmithKline) and VAQTA 50[®] (manufactured by Merck & Co., Inc.). Twinrix[®] (manufactured by GlaxoSmithKline) contains both HAV (in a lower dosage) and HBV antigens.³⁰ In Europe, only Twinrix[®] has been approved by the EMA for adults.³¹

Hepatitis A vaccines: efficacy and safety

HAV vaccine has been shown to be highly immunogenic in the general population. From 90 to 95% of those vaccinated will have detectable protective antibodies one month after 2 doses of an inactivated vaccine, and this may persist for a few decades.⁸⁸ Clinical trials in endemic countries have shown a high protective efficacy against clinical hepatitis, usually above 90% one year after the last dose of vaccine.^{95,96} The effectiveness of the HAV vaccine has been shown by marked reductions in disease incidence after the introduction of vaccination. Reported declines in HAV incidence are usually above 90% 5–10 y after the introduction of childhood immunization campaigns.⁹⁷⁻⁹⁹ The duration of protection has been under study since these vaccines were introduced in the 1990s, but antibodies have been shown to persist for at least 17 y in almost all children vaccinated with 2 doses of inactivated HAV vaccine in various studies.¹⁰⁰⁻¹⁰² Some authors have suggested that antibodies could persist for more than

45 y using a cut-off of ≥ 20 IU/L (the typical immunological threshold used to determine vaccine response).¹⁰³ The safety profile of inactivated HAV vaccines (all types) has been assessed in pre- and post-licensing trials and may be considered as excellent regardless of age at administration and the scheduled use.^{88,104,105} Pain and tenderness are the most common local adverse reactions at the injection site, occurring in approximately 50% of recipients,^{88,106,107} whereas fever and myalgias are the most common systemic adverse events.¹⁰⁷ No severe adverse events are usually reported following hepatitis A vaccination.

Immunological response after HAV vaccination in HIV-infected adults: associated factors

There is little data on the efficacy of the HAV vaccine in HIV-infected subjects, and the sample size of published studies is relatively small in order to measure the reduction in attack rates in vaccinated and unvaccinated populations. However, the immunogenicity of the HAV vaccine in HIV-infected subjects has been studied in populations with different characteristics, especially in the HAART era.¹⁰⁸⁻¹²⁰ The evidence comes mainly from RCTs and retrospective, observational studies. **Table 3** shows studies published in the HAART era that assessed the immunological response to HAV (studies which measured the vaccine response between 1 month and 1 y after the last dose). The heterogeneity of the methodology and study populations means the results must be interpreted with caution. The level of immunosuppression (measured by CD4 counts), the HIV RNA viral load, the vaccine schedule and sex have been associated with the vaccine response. HAV antibody seroconversion rates (after at least 2 doses of HAV vaccine) range from 48.5% to 93.9%.^{108,109} Thus, the immune response to the HAV vaccine is reduced in immunocompromised patients (both the proportion of subjects who seroconvert and the concentration of HAV antibody titres).¹¹¹

A weakened immune system has been associated with a poorer response to many vaccines¹²¹ and HAV is no exception. Higher CD4 counts are associated with a better vaccine response.^{108,110,117,119,120} The cut-off CD4 count for a better response differs between studies, but < 200 CD4 have been associated with poorer antibody seroconversion in several studies.^{110,116-118,120} Rimland et al. reported that patients with CD4 T-cell counts < 200 cells/mm³ were 16-times more likely to be nonresponders.¹¹⁰ A lower CD4/CD8 ratio has also been associated with a poorer response.¹¹⁹ Likewise, low HIV RNA viral loads lead to better vaccine response in HIV-infected adults.^{111,115}

The number of HAV doses received affects the vaccine response in HIV-infected patients. As in immunocompetent individuals, 2 doses of hepatitis A vaccine are more immunogenic than one.^{108,111,115,119,120} Studies comparing the vaccine response according to whether recipients received 2 or 3 doses of inactivated HAV vaccine found that both the proportion of responders and the GMT of HAV antibodies were higher after the third dose.^{112,115} However, this seems not to be the case when rapidly-accelerated schedules (day 0, 7 and 21) were used, at

Table 3. Studies assessing the immunological response after HAV vaccination in adults in the HAART era

Author / Year	Study design	Vaccine manufacturer and schedule	Baseline immunological status of participants	Response rate (%)*	Main findings [#]
Kemper et al. ^{1,20} 2003	RBDCT	HAVRIX 1440 EIU, Two doses, 6 months apart	CD4 count mean = 376 cells/mm ³	After the 1st dose: 11.1% (5/45) After the 2nd dose: 52.1% (25/48)	Protective antibody response to vaccination was associated with CD4 count \geq 200 cells/mm ³
Wallace et al. ¹⁰⁸ 2004	RBDCT	VAQTA 50 IU, Two doses, 6 months apart	CD4 count mean = 458 cells/mm ³ 76% on HAART	One month after the 1st dose: 61.0% (33/54) One month after the 2nd dose: 93.9% (46/49)	Protective antibody response to vaccination was associated with CD4 count \geq 300 cells/mm ³
Weissman et al. ¹⁰⁹ 2006	Retrospective	HAVRIX 1440 EIU, Two doses, 6–12 months apart	85% on HAART	After the 2nd dose: 48.5% (67/138)	Protective antibody response to vaccination was associated with female sex and higher CD4 count
Rimland D and Guest J.L. ¹¹⁰ 2005	Retrospective	HAVRIX 1440 EIU, Two doses	No data	After the 2nd dose: 60.7% (130/214)	Protective antibody response to vaccination was associated with higher CD4 count, especially if > 200 cells/mm ³
Overton et al. ¹¹¹ 2007	Retrospective	HAVRIX 1440 EIU, Two doses	CD4 count mean = 447 cells/mm ³ 68% on HAART	After the 1st or the 2nd dose: 49.6% (133/238) After the 2nd dose: 52.2% (94/180)	Protective antibody response to vaccination was associated with male sex and HIV viral RNA load < 1000 copies/ml
Launay et al. ¹¹² 2008	RCT	HAVRIX 1440 EIU, (a) 2 doses (6 months apart) vs. (b) 3 doses (0,1 and 6 months)	CD4 count median = 355 cells/mm ³ 95% on HAART	(a) After the 1st dose: 37.9% After the 2nd dose: 69.4%(34/49) (b) After the 3rd dose: 82.6% (38/46)	The 3-dose group induced a significantly higher antibody titer. Protective antibody response to vaccination with not smoking
Crum-Cianflone et al. ¹¹³ 2011	Retrospective	VAQTA 50 IU or HAVRIX 1440 EIU, Two doses (6–18 months apart)	CD4 count median = 461 cells/mm ³ 62% on HAART	After the 2nd dose: 89% (116/130)	Younger age was associated with a higher initial GMC, with a trend to lower log10 plasma HIV RNA levels with better response.
Kourkounti et al. ¹¹⁴ 2012	Prospective observational	HAVRIX 1440 EIU or VAQTA 50 IU, Two doses, 6–12 months apart	CD4 count median=564 cells/mm ³	After the 2nd dose: 74.4% (260/351)	Protective antibody response to vaccination was associated with higher CD4 count. A higher response rate and higher GMTs were observed in patients with CD4 counts \geq 500 cells/mm ³
Mena et al. ¹¹⁹ 2013	Retrospective	HAVRIX 1440 EIU, (a) One dose vs. (b) Two doses (6 months apart) vs. (c) Twinrix (720 EIU) at 0,7,14–21 d	CD4 count median=631 461 cells/mm ³ 64% on HAART	(a) 60.0% (48/80) (b) 80.7% (130/161) (c) 70.7% (29/41)	Protective antibody response to vaccination was associated with female sex, not HCV co-infection and a higher CD4/CD8 ratio. Higher response was associated with reception of 2 doses of standard schedule (in comparison with those receiving only one of those of the same schedule)

Tseng et al. ¹¹⁵ 2013	Prospective observational	HAVRIX 1440 EIU, (a) Two doses, 6 months apart vs. (b) 3 doses at 0,1 and 6 months	All participants were MSM (a) CD4 count mean = 538 cells/mm ³ at baseline. 67% on HAART (b) CD4 count mean = 452 cells/mm ³ at baseline. 58% on HAART	At week 24 after the first dose: (a) 88.6% (109/123) (b) 89.2% (182/204)	The GMC of anti-HAV antibody for 3-dose subjects were significantly higher than for 2-dose subjects, but was lower than HIV-uninfected subjects. Protective antibody response to vaccination was associated with higher CD4 counts and undetectable plasma HIV RNA load
Jimenez et al. ¹¹⁶ 2013	Retrospective	(a) HAVRIX 1440 EIU, Two doses, 6 months apart vs. (b) Twinrix 720 EIU, at 0,1, and 6 months	(a) HAVRIX Responders: CD4 count median = 401 cells/mm ³ Non-Responders: CD4 count median = 362 cells/mm ³ (b) Twinrix Responders: CD4 count median = 511 cells/mm ³ Non-Responders: CD4 count median = 378 cells/mm ³	(a) 54% (67/125) (b) 53% (54/101)	Protective antibody response to vaccination was associated with higher baseline median CD4 counts and lower median HIV RNA levels. Patients with CD4 counts \geq 350 cells/mm ³ were more likely to respond than those with CD4 counts <200 cells/mm ³ . Responders were more likely to be virologically suppressed. Twinrix receivers were less likely to respond if vaccination series was not completed
Kourkounti et al. ¹¹⁷ 2013	Prospective observational	HAVRIX 1440 EIU or VAQTA 50 IU. Two doses, 6-12 months apart	CD4 count median = 570 cells/mm ³ 56% on HAART	After the second dose: 77.0% (87/113)	Protective antibody response to vaccination was associated with higher baseline median CD4 count at vaccination. The count of other immune cells or the administration of antiretroviral therapy did not predict response to HAV vaccine in HIV patients with baseline CD4 count >200 cells/mm ³
Jablonska et al. ¹¹⁸ 2014	Prospective observational	HAVRIX 1440 EIU. Two doses, 6 months apart	CD4 count median = 450 cells/mm ³ 40% on HAART	79.5% (66/83) Five years after vaccination: 75.5% (37/49)	Protective antibody response to vaccination was associated with the absence of HCV antibodies. Most HIV-infected adults with high CD4 counts had a durable response even up to 5 y after vaccination.

Inclusion and exclusion criteria: Appendix 2.

*Protective titre: Anti-HAV \geq 10 IU/L; Wallace et al., Crum-Cianflone et al.; \geq 18 IU/L; Weissman et al.; \geq 20 IU/L; Rimland and Guest, Launay et al., Kourkounti et al., Mena et al., Tseng et al. Kourkounti et al., Jablonowska et al.; \geq 33 IU/L; Kemper et al.; Not reported; Overton et al.; Jimenez et al.

#Associated factors in a multivariate analysis / Factors at baseline.

-RCT: Randomized Controlled Trial. RDBCT: Randomized Double-Blind Controlled Trial. GMT: Geometric Mean Titre. EIU: ELISA units. Anti-HAV: Antibody against hepatitis A virus.

these were associated with a lower response in comparison with patients receiving 2 doses of 6 months apart.¹¹⁹

Hepatitis C virus (HCV) coinfection was associated with a lower probability of response.¹¹⁹ In fact, coinfection with the HCV has been found to be a prognostic factor for non-response to HAV vaccination in patients with CD4 counts < 200 cells/mm³.¹¹⁸ This association has also been described in the case of HBV vaccination.¹²² Although more studies are needed to elucidate the immune mechanisms explaining a poorer vaccine response in HIV/HCV infected subjects, it has been suggested that this co-infection results in dendritic cell dysfunction that may impair antigen presentation and thus affect the response to vaccination.

Sex has intermittently been associated with the vaccine response in different studies. Three retrospective studies reported that males were less likely to be responders,^{109,111,119} although Armstrong et al. reported an inverse association.¹²³ One study found that not smoking was associated with a better response to the HAV vaccine in HIV infected adults,¹¹² something already observed in immunocompetent HBV vaccine recipients.¹²⁴ The mechanisms explaining the effect of smoking on the vaccine response remain to be elucidated.

Long-term persistence of protective levels of IgG anti-VHA

Few studies have assessed the duration of protection provided by HAV vaccination in HIV-infected adults. A retrospective study by Crum-Cianflone et al. found that, in patients with well-controlled HIV infections who responded to initial vaccination, there was evidence of antibody persistence almost 10 y later (90% after 3 y and 85% after 6–10 years).¹¹³ A prospective study by Kerneis et al., showed persistence of antibodies in 85% of patients after almost 4 y of follow up.¹²⁵ Finally, a Polish study by Jablonowska et al. found that 75% of HIV-infected subjects who responded to initial vaccination had detectable antibodies 5 y after vaccination.¹¹⁸ The duration of protection has been associated with suppressed HIV RNA levels at vaccination.^{113,125}

Safety of HAV vaccination in HIV-infected adults

Limited data from randomized clinical trials is available on the safety of HAV vaccines in HIV-infected patients.^{108,112,120,126,127} However, no serious adverse events are usually reported after HAV vaccination regardless of the number of doses or the immunological status,¹²⁰ and vaccination has no effect on the course of HIV infection.¹²⁷ Adverse events are usually minor, although local reaction at the injection site are frequently reported.¹⁰⁸ The most frequent local adverse events reported are pain and soreness. Mild systemic events such as headache and fever have also been reported.¹⁰⁸ The frequency and nature of adverse events following HAV vaccination is similar to placebo.¹²⁰ Serious adverse events following HIV vaccination in HIV-infected subjects have seldom been reported.

Current recommendations on hepatitis A vaccination for HIV-infected patients

Routine HAV vaccination of susceptible HIV-infected individuals is not widely accepted. Both the CDC and WHO recommend vaccinating these subjects if any other medical, behavioral, epidemiological or occupational condition is added to HIV infection.^{88,128} These conditions usually include: persons traveling to or working in countries with high or intermediate HAV endemicity, MSM, users of injectable drugs, persons with chronic liver disease, including hepatitis B or C, people with clotting factor diseases, immunosuppressed persons who have undergone transplantation, and contacts of children arriving from countries with high or intermediate HAV endemicity. The US Guidelines for prevention and treatment of opportunistic infections in HIV-Infected adults and adolescents, BHIVA guidelines for the immunization of HIV-infected adults and the clinical guidelines of the EACS also support these recommendations.^{79,81}

The currently-accepted global schedule is 2 doses separated by 6–12 months. In HIV patients considered at risk, the BHIVA guidelines mention the option of vaccinating with a 3-dose schedule administered within a maximum of 12 months, but only in subjects with a CD4 lymphocyte count < 300 cells/mm³.⁸⁰

Of the institutional recommendations reviewed, only the UK Green Book on immunisation against infectious diseases guidance mentions revaccination when primary vaccination does not produce a protective response.¹²⁹

The EACS recommends periodic controls of antibody titres in vaccinated immunocompromised subjects.⁸¹ The BHIVA recommends a booster vaccine dose every 5 y (both bodies indicate vaccination in patients at risk of contracting hepatitis A).⁸⁰

Concluding Remarks

The response to HBV and HAV vaccination is suboptimal in HIV-infected subjects. The factors most frequently associated with a deficient level of antibodies after vaccination are mainly those related to immunosuppression (CD4 level and HIV RNA viral load) and to the frequency of administration and/or the amount of antigenic load in the doses. Furthermore, the studies reviewed support the idea that the duration of the response is worse than in HIV-free individuals. The duration of the response to both HBV and HAV vaccines is associated with suppression of the viral load at vaccination and, in the case of HBV vaccination, is also associated with a higher antibody level after vaccination. In terms of safety, there is no evidence of more, or different, adverse effects compared with HIV-free individuals (Tables 2 and 3).

With respect to the indications for HBV vaccination in HIV-infected adults, the default international recommendation remains the administration of 3 doses at 0, 1 and 6 months. The measures most frequently suggested in order to manage and improve the response to vaccination are: starting HAART before vaccination for patients with a CD4 cell count <200 cells/mm³

and ongoing HIV viral replication,⁸¹ serologic determination of antibodies after administration of the last dose of vaccine,^{79,80} re-vaccination when concentrations of anti-HBs of 10 IU/L are not reached after primary vaccination,^{29,79,81} and annual serological testing for those who have previously responded to vaccination.^{79,80}

Primary vaccination with a higher number of doses or a higher concentration of HBsAg per dose has not been recommended by any of the previously-mentioned institutions or associations.

In contrast to hepatitis B, routine HAV vaccination of susceptible HIV-infected adults is not widely accepted. Both the CDC and WHO recommend vaccinating these subjects if any other medical, behavioral, epidemiological or occupational condition is added to HIV infection.^{88,128} These conditions usually include: persons traveling to or working in countries that have high or intermediate HAV endemicity, MSM, injection drug users, persons with chronic liver disease, including hepatitis B or C, people with clotting factor diseases, immunosuppressed persons who have undergone transplantation and contacts of children arriving from countries with high or intermediate HAV endemicity. The US Guidelines for prevention and treatment of opportunistic infections in HIV-Infected adults and adolescents, the BHIVA guidelines for the immunization of HIV-infected adults and the clinical guidelines of the EACS also support these recommendations.⁷⁹⁻⁸¹

In HIV-infected subjects who present any of the previously-mentioned indications, the most widely recommended vaccination schedule is 2 doses separated by 6–12 months. Of the institutional recommendations reviewed, only the UK Green Book on immunisation against infectious diseases guidance mentions revaccination when primary vaccination does not produce a protective response.¹²⁹ Periodic control of antibody titres in vaccinated immunocompromised subjects,⁸¹ the administration of a

booster dose every 5 years⁸⁰ and vaccination with a 3-dose schedule within a maximum of 12 months in subjects with a CD4 count <300 cells/mm³,⁸⁰ are other strategies proposed for the control and improvement of the response to HAV vaccination in HIV-infected adults.

There is a substantial difference in the recommendations made by the main associations and international health bodies on the management of viral hepatitis vaccination in people living with HIV. Despite literature-based advice with respect to the administration of alternative schedules, revaccination after the failure of primary vaccination, and the need for periodic re-evaluation of antibody levels, few firm systematic recommendations are found in the leading Guidelines. The large amount of scientific literature on the subject of hepatitis vaccination in HIV-infected subjects, especially HBV vaccination, should form the basis of international consensual clinical guidelines that take into account the diversity of patients living with HIV when administering conventional vaccination or evaluating alternative ones that may be useful in specific cases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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