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Non-Responsiveness to Hepatitis B Vaccination in HIV Seropositive Patients; Possible Causes and Solutions

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Abstract

Hyporesponsiveness (anti-HBs 10-100 IU/l) or non-responsiveness (anti-HBs < 10 IU/l) to hepatitis B vaccines is a problem in approximately 20-70% of HIV-positive patients. Mechanisms for impaired humoral and cellular immunity related to the HIV infection are reviewed.
Contributing risk factors like age, gender, CD4+ T-cell count, HIV RNA load and coinfection with hepatitis C are highlighted. New developments in improving the HBV vaccine immunogenicity are discussed and clinical recommendations are given for HBV-re-vaccination of HIV patients who failed on standard HBV vaccination. **(AIDS Rev. 2009;11:157-64)**
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Introduction

Worldwide, but especially in sub-Saharan Africa and East Asia, millions of people are coinfected with HIV and hepatitis B virus (HBV). The HIV and HBV infections often occur simultaneously due to the shared modes of transmission[1-3]. The HBV infection progresses more aggressively in HIV-coinfected patients, with a higher incidence of cirrhosis and hepatocellular carcinoma[4]. On the other hand, it is suggested that HBV is a cofactor for HIV disease progression[3]. The risk of hepatotoxic side effects of combined antiretroviral therapy (cART) is increased in patients with HBV coinfection[3,5-7].

An HBV vaccination of seronegative people can prevent hepatitis B infection and its sequelae[2,8]. However, after a three-dose (0, 1, 6 months) vaccination schedule, vaccination against HBV is not as effective in HIV-positive as it is in HIV-negative persons[9-12]. Around 90-95% of healthy adult individuals are protected after vaccination, whereas 20-70% of the HIV-seropositive patients develop protective antibody titers, mostly depending on CD4+ T-cell counts and HIV viral loads[9].

Recommendations have been published for the vaccination of non-responders to hepatitis B vaccines with chronic kidney disease and for those on dialysis[13], but none exist for the HIV-infected patient. Soriano, et al. published an article with recommendations from an HIV-HBV international panel in 2005, partly based on the work of Tedaldi, et al.[14], advising vaccination with hepatitis B vaccine when CD4+ numbers are greater than 200 cells/µl and, when they are not, to start cART first[3].

Because some recommendations for vaccination on other immunocompromised groups of patients may be of use for vaccinating HIV-infected patients, these groups will be discussed briefly.

In this review, the probable underlying reasons for hypo- and non-responsiveness to HBV vaccination in HIV-infected patients are summarized. The focus will lie on immunologic, genetic, and individual factors. Recommendations are given for effective HBV vaccination of HIV-infected patients.

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Possible causes for hyporesponsiveness to HBV vaccination

HIV infection-related factors

HIV infection has profound effects on the immune system and comprehensive reviews have been written on HIV pathogenesis[15-17].

Characteristic is a progressive loss of $CD4^+$ T helper (Th) cells in the blood compartment, ultimately causing susceptibility to opportunistic infections and the development of AIDS[18]. This decline in $CD4^+$ T-cell numbers is due to several mechanisms: cell death caused by infection by HIV itself, chronic immune activation leading to apoptosis, antibody-dependent cell-mediated cytotoxicity killing of $CD4^+$ cells carrying gp120, and impaired lymphocyte regeneration[15-17].

More recent insights show that degradation of the immune system already starts during acute HIV infection, and comprises extensive $CD4^+$ memory T-cell destruction in extra-lymphoid effector sites and, subsequently, of its precursors, central memory and/or naive T-cells in the secondary lymphoid tissues[18]. Furthermore, other dysfunctions of the immune system develop that equalize aging, such as increased numbers of $CD28^-$ $CD8^+$ T-cells, an oligoclonal instead of a polyclonal T-cell repertoire, and reduced numbers of interferon gamma (IFNγ) producing virus-specific T-cells upon antigen stimulation[19]. Moreover, a hyperimmune activation status and dominating T-cell activation specific for particular HIV-epitopes and less for other epitopes like HBV will diminish the degree of response to vaccination[18].

A lack of $CD4^+$ T-cell help can impair $CD8^+$ T-cell and B-cell activity, resulting in hampered cytotoxicity and antibody production, while the inability to mount a virus-specific $CD8^+$ T-cell response results in a level of circulating virus that cannot be cleared by antibodies alone[20].

Furthermore, it is proposed that the persistence of HIV particles provides a chronic stimulus for mechanisms normally associated with innate immune responses, and that chronic innate immune activation suppresses functional T-cell-mediated adaptive immune responses while sustaining the activated phenotype of T-cells[21].

HIV viral load

The production of hepatitis B-specific antibody inversibly correlates with HIV RNA load. Persons with undetectable viral load have a higher chance of having a protective antibody titer after HBV vaccination[22-24], suggesting that ongoing viremia limits successful vaccination[23].

Mounting an appropriate immune response depends on the strict regulation of lymphocyte activation; to become activated, lymphocytes need at least two independent signals[25,26]. The first is an antigen-specific signal sent via the T-cell receptor, uniquely present on T-cells, or via the surface immunoglobulin on B-cells. The second, co-stimulatory, signal is independent of the antigen receptor and is crucial for full activation, sustained cell proliferation, the prevention of anergy or apoptosis, induction of differentiation to effector and memory status, and for cell-cell cooperation. These molecules are transmembrane proteins that induce an intracellular signaling cascade via their cytoplasmic tail that modifies the T-cell receptor-mediated signal in a stimulatory or an inhibitory way[25,26]. An important receptor/ligand pair in T/B-cell cooperation for instance is CD40/CD40L. Signaling of CD40 is crucial for antibody production, isotype-switching, upregulation of surface molecules, development of germinal centers, and the humoral memory response[27,28].

$CD4^+$ cells

A critical number of $CD4^+$ cells are necessary in HIV-infected subjects to mount an appropriate immune response. This number varies between 150-500 cells/mm^3 in different studies[29]. The large variation between these number could lie in the fact that HIV affects the immune system at an early stage of infection before $CD4^+$ T-cell numbers begin to decline[18,30].

Pasricha, et al. found a 100% response after a three doubled-dose vaccination schedule in 27 HIV-positive patients with > 200 $CD4^+$ cells/mm^3 count[10]. Protection was only achieved in 47% of 13 patients with < 200 cells/mm^3 $CD4^+$ T-cell count[10].

The absence of a humoral-specific response to hepatitis B surface antigen (HBsAg) may be partly the result of the inability of $CD4^+$ T-cells to activate B-cells into isotype-switching of immunoglobulins due to a diminished CD40L expression on these T-cells in HIV-infected patients[31].

Moir, et al., on the other hand, claimed that viremia has no impact on the capacity of $CD4^+$ T-cells to express CD40L, but causes B-cells to poorly proliferate, correlating with reduced induction of interleukin 2 receptor (IL-2R) on their cell surface[32].

B-cells

In healthy individuals, a good response to HBV vaccination is correlated with a significant increase in the number of specific B lymphocytes[33].

Furthermore, a dominant Th1/0-like cytokine secretion pattern of HBs-specific T-cells exists also in chronic HBV-infected patients[34]. Incubation with IFNγ results in a dose-dependent expansion of the number of anti-HBs antibody secreting B-cells, so it can be concluded that Th1-like cells are crucial for the production of neutralizing anti-HBs antibodies and for effective virus control in acute hepatitis B infection and could be therapeutic in chronic HBV-infected patients[34].

Moir, et al., on the other hand, describe the B-cell defects in patients with HIV viremia, including hypergammaglobulinemia, increased expression of activation markers, increased levels of autoantibodies, higher risk of B-cell lymphomas, decreased responsiveness (*in vivo*) to vaccination and (*ex vivo*) stimulation. So, not only does HIV infection scale down $CD4^+$ T-cell help, but it causes intrinsic B-cell defects as well[32,35]. These defects ameliorate on cART[35].

Natural killer cells and natural killer T-cells

Natural killer (NK) and natural killer T (NKT) cells are considered mediators of vaccine response at the innate level. Their activation can mediate viral clearance and enhance the activation of adaptive components, together contributing to protection against hepatitis B infection[36-38]. A diminished activation of NK and NKT cells was found in healthy nonresponders to HBV vaccine, suggesting that NK and NKT cells are in fact important components of the protective immune response elicited by the vaccine[36].

Natural killer T-cells display an extremely restricted T-cell receptor repertoire consisting of a Vα24 chain preferentially paired to Vβ11[39], but circulating numbers of the $V\alpha24^+V\beta11^+$ subset of NKT cells seem to be reduced in HIV-infected subjects[40], possibly leading to quantitatively diminished responses to vaccination in this patient group.

Host-related factors

Human leukocyte antigen

The diversity of human leukocyte antigen (HLA) class II restriction elements involved in HBsAg presentation clearly differ between good and poor responders. The T-cells from good responders recognize HBsAg in the context of most of the available class II molecules. In poor responders, however, less HLA class II molecules participate in the HBsAg-specific T-cell response: Poor responders are frequently homozygous for certain HLA-DR, -DP, and -DQ molecules[41-43]. Furthermore, the proportion of HLA DRB1*07 is two- to sixfold higher in non-responders than in responders[41,43].

Little is known about ethnicity and vaccine response. A correlation was found between being indigenous Taiwanese and having a nonresponse to a booster vaccination with Engerix-B[44,45].

Gender

In one study in 144 HIV-infected patients who were revaccinated because of nonresponse (anti-HBs titer of 0 IU/l) after a standard vaccination schedule, more female than male patients had an adequate response (OR: 2.8 female/male; 95% CI: 1.3-6.3; p = 0.009). This was not associated with a difference in body mass index in men and women[46].

Age

Neither the total number of B-cells nor the number of Ig-secreting B-cells decreases with age, but a change in B-cell repertoire with respect to antigen specificity occurs. This increases the risk of nonresponse to HBV vaccine[47].

There is evidence of an immune dysregulation of T-cells in the elderly, including lower proliferative responses, resulting in altered help for B-cells and, henceforth, altered antibody production[47,48]. This occurs in the mucosal immune system earlier than in the systemic immune compartment[49]. Non-responsiveness increases with increasing age from 30 years onward[50]. Adding an additional dose of vaccine or changing the route of vaccination does not change this risk[50,51].

Pregnancy

Pregnancy is not a contra-indication for vaccination with hepatitis B vaccine (see www.rivm.nl for standard protocol) and there is no review on impaired responsiveness to vaccination with hepatitis B vaccine, even though immunity in pregnancy is modified; the innate immune system is activated and the adaptive immune system is suppressed[52].

Other factors

Coinfection with HCV

Rockstroh finds no evidence for differences in HIV-related mortality between hepatitis C virus (HCV)-coinfected cART-treated individuals[53], but Jones mentions a growing consensus that HCV has a deleterious effect on HIV progression[54]. Treatment therapies for HCV/HIV-coinfected patients are discussed by Cooper[55].

Antibody concentrations following vaccination for hepatitis A[56] and hepatitis B[57] are lower in HCV-infected patients than in HCV-seronegative individuals, but a high-dose booster is effective for the hepatitis B vaccine[57].

Antiretroviral therapy

Overton, et al, found that vaccinated responders received cART for a median of 13.5 months (interquartile range [IQR] 6.1-19.4 months), whereas treated nonresponders received cART for a median of 3.7 months (IQR 1.3-15.5 months; p = 0.005)[23]. It suggests that the duration of cART, through the improvement of cellular immunity, plays an important role in a successful response to vaccination, even after having AIDS before starting cART[58].

Combination ART reduces the chronic immune activation, leading to repopulation of both memory and naive T-cell subpopulations and $CD4^+$ $CD28^+$ lymphocytes in the blood compartment by shutting down viral replication. It causes reduction of abnormal T-cell activation, restoration of antigen-specific T-cell responses and normalization of T-cell repertoire[59]. Thymic T-cell production contributes to naive T-cell recovery at all ages during long-term successful cART, without signs of increased T-cell aging[60]. Also, immune reconstitution mediated by cART is not restricted to conventional $CD4^+$ and $CD8^+$ T-cells, but also involves reconstitution of an important immunoregulatory axis represented by CD1d and NKT cells[26,61].

Possible solutions

Type of vaccine

Recombivax-HB®, Engerix-B®

The current recombinant vaccines, Recombivax-HB® (Merck) and Engerix-B® (GlaxoSmithKline), are yeast-derived and produced by genetic engineering methods[62]. They contain a single antigen (S) and are evenly protective against disease from hepatitis B virus, although Engerix-B® gives a higher geometrical mean titer when measured in adolescent and adult populations[62,63].

Twinrix®

Instead of using a vaccine with more than one antigen, two different hepatitis vaccines can be combined, as is the case with Twinrix® Adult (GlaxoSmithKline). This vaccine contains 720 ELISA units of inactivated hepatitis A virus (HAV) antigen and 20 µg HBsAg (Havrix®, GlaxoSmithKline, and Engerix-B®)[64].

A stronger and faster anti-HAV or anti-HBsAg response can be achieved when changing over from monovalent to combined vaccination, regardless of when this switchover is performed during the vaccination schedule[64]. Revaccination of healthy nonresponders to the standard hepatitis B vaccine regimen with a double dose of Twinrix®, given at 0, 1, and 6 months, is effective in 95% of the cases[65], though both anti-HBs and anti-HAV titers are significantly lower in the nonresponder group than in the reference group[65].

HepaCare®

Novel recombinant vaccines have been produced that contain three antigens (S, pre-S1, and pre-S2) and are called triple-antigen vaccines. One of them was HepaCare®. The potential added value of this novel vaccine has been evaluated by comparing Recombivax-HB® with Hepacare® and the conclusion was that the latter was statistically equally efficient in a two-dose regimen, and superior in a three dose regimen, to Recombivax-HB®[66,67]. Both vaccines are well tolerated and have similar safety profiles[66,67].

These vaccines have been compared in healthy individuals, but prove to be superior for individuals who are at risk for suboptimal response to vaccination (advancing age, obesity, smoking)[66,67]. This was endorsed in a double-blind, randomized, controlled study on healthcare workers who had failed to respond adequately to a course of hepatitis B vaccination with a current vaccine[68]. There was a significantly faster and greater response to revaccination with HepaCare® than to revaccination with Engerix-B®[68].

The marketing authorization of HepaCare® has been withdrawn.

Dosing and vaccination schedules

For patients on hemodialysis and for patients with general immune suppression, a double dose of Engerix-B® or Recombivax-HB® given on a standard schedule (i.e. 0, 1, and 6 months) is recommended[13]. Vaccine dosage has not been defined in HIV-infected adults and children.

The vaccine efficacy may be increased by doubling the pediatric dosage of 10 µg in HIV-infected children to the adult dose of 20 µg[69].

Rey, et al. tested the effect of doubling the number of vaccinations of adults by adding three booster doses to a three-dose (T 0, 1, 2) vaccination[11]. They suggested that doubling the number of hepatitis B vaccinations in HIV-infected patients can significantly improve anti-HBs response rates[11]. However, Cornejo-Juárez, et al. found no difference in a small randomized controlled trial comparing a 20 µg dose to a 40 µg dose in three administrations[70]. They did find a significantly higher seroconversion rate for patients with CD4 cell counts > 200 cell/mm^3, compared to those with cell counts of < 200 cell/mm^3 [70]. In another randomized controlled trial in 210 subjects, a double vaccination dose improved the immunologic response to the vaccine only in patients with a CD4$^+$ cell count > 350 cell/mm^3 and a HIV viral load of < 10,000 copies/ml[71].

Double-dose hepatitis B virus revaccination of HIV-infected patients proved to be effective in 50.7% of 144 patients who had previously failed to respond to standard doses[46].

The usual adult dose (20 µg each dose) as compared to 40 µg of Engerix-B® recombinant vaccine is inferior in end-stage renal disease patients. Besides, further increasing the dose to 80 µg is suggested because long-term results show that the 80 µg regimen is associated with significantly greater persistence of anti-HBsAg[72].

The currently recommended dose of recombinant hepatitis B vaccine in patients with end-stage liver (and renal) disease awaiting transplantation is at least three doses of 40 µg. In order to obtain the best response, this should be given as early as possible in the course of disease[73].

Routes of vaccination/injection

Several studies have investigated routes other than intramuscular deltoid injection for vaccination. Intradermal vaccination was mainly studied in (end-stage) renal failure patients. Only one study on intradermal vaccination in HIV-infected subjects was performed. The dose of an intradermal vaccination is approximately one-tenth of that of an intramuscular vaccination, which makes it more cost-effective while equally immunogenic. The intradermal immunization assessed in the study induced protective immunity among HIV-positive subjects (in 39%), as has often been described to occur with intramuscular immunization[74]. So, from this study it can be concluded that intradermal vaccination is equally effective, but less practical than intramuscular vaccination because of the number of injections that needs to be given[75] in order to reach protective titers and to maintain them over follow-up[76].

Adjuvants

Adjuvants augment antigen-specific immune responses by physical localization and improved presentation of antigen and by provocation of inflammatory or innate immune responses. At the moment, the adjuvants as mentioned below are only in used in the setting of clinical trials.

Newer adjuvants

Cytosine-phosphate-guanine (CpG) oligodeoxynucleotides (ODN) represent a new type of adjuvant that has shown promise in primate models and initial clinical trials[77].

Synthetic ODN containing un-methylated CpG motifs are potent direct stimulants of B-cells and plasmacytoid dendritic cells through binding to the innate immune receptor toll-like receptor 9 (TLR9), which activates an immunostimulatory cascade and can indirectly, through secretion from these cells, also activate a number of other types of immune cells[24,78].

The CpG ODN improves the humoral immune response to Engerix-B® in simian immunodeficiency virus (SIV)-infected rhesus macaques[24], but HIV RNA and antibody titers were inversely correlated. The antibody titers were about 1_{log}-fold lower in the infected than in the healthy macaques[9,24].

The results of a randomized, controlled, double-blind, phase Ib/IIa study suggest that in subjects with compromised T-helper function, *in vivo* TLR9 stimulation can substitute for the normal requirement for T-cell help in generating humoral immunity[78-80].

Generally, CPG 7909 added to an accelerated double-dose of Engerix-B® vaccine achieved superior results in time to seroconversion and seroprotection of cART-treated HIV-infected persons[80]. Absolute anti-HBs

titers and durability of response is also better compared to other novel adjuvants like monophosphoryl lipid A (MPL), thymopentin, AM3 (Immunoferon®; Cantabria Pharma) and levamisole according to Cooper[79]. Comparable results were achieved by Halperin, et al., who used an immunostimulatory DNA sequence (ISS 1018) plus HBsAg vaccine in healthy adults[81].

Enhancement of cell-mediated immune responses have been recognized as an important factor in the clearance of acute infection, and for that reason Cooper suggest a potential role for CPG 7909 in therapeutic vaccines for HBV as well[79]. It may be possible to develop a two-dose vaccine with CpG adjuvant that would be superior to the current three-dose vaccines[77,81].

DNA vaccines

Another novel vaccine approach for rapid induction of strong Th1 immunity that seemed promising in animal models is DNA-based immunization. Engerix-B®/CpG ODN was compared with Engerix-B®/DNA-vaccine[77].

The HBsAg-expressing DNA vaccine alone did not give any detectable anti-HBs levels[77]. After challenge, however, one of the animals appeared to be protected, despite the lack of detectable pre-challenge anti-HBs, suggesting priming of an antibody response[77]. For now, DNA vaccines are still part of the future.

Cytokines

In HIV-infected persons, the basal cytokine levels appear to be different from those in healthy controls, so another possibility to augment immune response to HBV vaccines could be to use exogenous interleukins or interferons as adjuvants, particularly IL-12 and IL-4 as suggested by Wang, et al.[43] because *IL-12B* promoter S allele was the only cytokine gene variant associated with the nonresponder phenotype ($p = 0.03$)[43]. Associations between IL-4 variants have been associated with functional consequences and clinical manifestations in certain infectious diseases[43].

Interleukin 2 could be of clinical importance as well, because Meuer, et al, suggests that low-dose IL-2 treatment is an efficient means of inducing systemic antigen-specific immune responses in immunodeficient (hemodialysis) subjects. The optimum dose of IL-2 and the time point for vaccination need to be determined[82].

Interleukin 2 therapy has no immune-enhancing effect on the induction of a primary response, but increases the frequency of IFNγ-producing memory cells after booster immunization[83].

Granulocyte-macrophage colony-stimulation factor

Patients with end-stage renal disease often show inadequate response to hepatitis B vaccination. Several articles have been published about the positive effect of granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjuvant for hepatitis B vaccination. This is true for revaccination as well as primary vaccination in these patients[84-92].

Sasaki, et al. investigated the effect of recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) as an adjuvant for the hepatitis B vaccine in HIV-infected patients and concluded that the use of rhGM-CSF enhances the efficacy of HBV vaccine in HIV-infected patients[93].

Passive immunization

Patients treated for acute lymphoblastic leukemia in the ages of 1-21 years cannot be protected from hepatitis B infection by vaccination alone, nor by vaccination combined with interferon α2b[94]. Combining passive (human-specific hepatitis B immunoglobulin) and active immunization, or preceding the active immunization by passive immunization, significantly increases the response rate in these patients[94].

Clinical recommendations for optimal HBV vaccination

An HBV vaccination should be offered to all HIV-positive patients who are at risk for acquiring HBV infection and who have negative HBsAg and anti-HBc serological results. The younger the patient, the better the response, as the vaccine response significantly declines with age[47-51]. Preferably, patients should have CD4 counts > 200 cells/ml and undetectable HIV-RNA[10,22-24,29] Therefore, when applicable, vaccination is offered at least six months after initiation of cART. Initial vaccination optimally consists of three doses of 10 µg HBvaxPRO® (Merck) intramuscularly in the deltoid region[13]. Nonresponders, defined as having an anti-HBs antibody concentration of less than 10 IU/l one month after the last vaccination, should be revaccinated with a double dose of 20 µg HBvaxPRO® again at 0, 1, and 6 months.

In case of persistent non-responsiveness, revaccination with three double-dose Engerix-B® can be offered and may give a positive response[13,46,69-72]. A recently

published study showed a > 95% efficacy with complete revaccination with a double dose of Twinrix® [65].

Suggestions for further research

It is difficult to find the best way to vaccinate HIV-positive patients because systematic trials comparing different immune status, vaccines, doses, and other factors are scarce, making it necessary to compare different types of studies.

A systematic review should be made on specific immunological aspects of HIV positivity in relation to immunizations. This includes defining the cut-off value of the number of $CD4^+$ cells necessary for adequate immune response to vaccination with hepatitis B vaccine in HIV-infected patients. Then, the most effective vaccination dose and schedule should be determined, including the use of available adjuvants, if possible.

On top of this, non-HIV-specific aspects of non-responsiveness to vaccination need to be assessed for an optimal approach in the HIV-infected patients.

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