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**Hepatitis B vaccine by intradermal route in non responder patients: An update**

Filippelli M *et al*. Hepatitis B vaccine by intradermal route in non responders

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**Abstract**

Vaccination is the main prophylactic measure to reduce the mortality caused by hepatitis B virus (HBV) infection in healthy subjects since the immune response to hepatitis B recombinant vaccination occurs in over 90% of general population. Individuals who develop an anti-HBs titer less than 10 mIU/mL after primary vaccination cycle are defined “no responders”. Many factors could cause a non response to the HBV vaccination, such as administration of the vaccine in buttocks, impaired vaccine storage conditions, drug abuse, smoking, infections and obesity. Moreover there are some diseases, like chronic kidney disease,human immunodeficiency virus infection, chronic liver disease, celiac disease, thalassaemia, type I diabetes mellitus, down’s syndrome and other forms of mental retardation that are characterized by a poorer response to HBV vaccination than healthy subjects. To date it is still unclear how to treat this group of patients at high risk of hepatitis B infection. Recent studies seem to indicate that the administration of HBV recombinant vaccine by the intradermal route is very effective and could represent a more useful strategy than intramuscular route. This review focuses on the use of anti hepatitis B vaccine by intradermal route as alternative to conventional intramuscular vaccine in all non responder patients. A comprehensive review of the literature using PubMed database, with appropriate terms, was undertaken for articles in English published since 1983. The literature search was undertaken in September 2013.

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**Key words:** Hepatitis B virus; Vaccine; Intradermal route; Non responders; Update

**Core tip:** Vaccination is the principal strategy to reduce the morbidity and mortality caused by hepatitis B virus. Vaccinated subjects with an hepatitis B surface antibody titer less than 10 mIU/mL after primary vaccine series are considered “no responders”. There are chronic conditions that are characterized by a poorer response to hepatitis B virus vaccination than healthy subjects. To date it is still unclear how to treat this group of patients at high risk of hepatitis B infection. This review focuses on the use of anti hepatitis B vaccine by intradermal route as alternative to conventional intramuscular vaccine in all non responder patients.

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**INTRODUCTION**

More than 1012 of people in the globe are infected by hepatitis B virus (HBV), of which more than 400 million become chronic carriers and more than 700000 individuals die annually due to complications caused by acute or chronic HBV infection[1,2]. In spite of improvements in hygienic conditions and in anti-viral therapy, eradication of HBV has not been obtained and to date vaccination is the only strategy to prevent this infection[1]. Since HBV vaccination was introduced, many advances (e.g use of recombinant technology) have been made in order to increase its safety and immunogenicity[3]. HBV vaccination is able to stimulate a long-term immune response in healthy individuals, since the antibody response occurs in over 90% of the immune-competent individuals after three doses of 20 μg HBV vaccine administered at 0, 1, and 6 mo intervals[4,5]. Considering this percentage of vaccine efficacy in healthy subjects, it has been postulated that between 537000 and 660000 HBV-related deaths could be prevented each year with a mass vaccination[6]. For this reason health authorities in the world suggest to vaccinate also all people with chronic conditions[1,7,8].

A sero-protection response is defined by an hepatitis B surface antibody (anti-HBs) titer ≥ 100 IU/L. An anti-HBs titer > 10 IU/L is considered as a “protective” titer, although it could not confer protection after HBV contact in every case (poor response)[9,10].

Individuals who develop an anti-HBs titer less than 10 mIU/mL after three doses of vaccine are defined “no responders”. Many factors could cause a non response to the HBV vaccination, such as administration of the vaccine in buttocks, impaired vaccine storage conditions, drug abuse, smoking, infections and obesity[11]. In recent years it has been suggested an important role of genetic factors in predisposing to hepatitis B vaccine unresponsiveness. This factors are represented by specific human leukocyte antigen (HLA) haplotypes and specific single nucleotide polymorphism in genes of cytokine or cytokine receptors and toll like receptors[12,13].

The unresponsiveness to hepatitis B vaccination is an important problem, because non-responder subjects represent a great container of HBV-carriers. This problem led the researchers to propose new immunization strategies in order to reach the “universal protection”.

**INTRADERMAL ROUTE VACCINATION: THE RATIONAL**

Many vaccines are administered by intramuscular route although the muscle is a poorly immunogenic organ[14,15]. On the other hand the skin is a more immunogenic site for vaccination due to presence in the dermis of dendritic cells, capable of presenting antigens and stimulating innate and adaptive immune responses. In fact skin protects the body from microbial infection using both its physical barrier and its immunological function performed by dendritic cells[16].

The main target of intradermal vaccination is represented by Langerhans cells and macrophages in the dermis that are specialized in antigen presentation due to their ability to express high levels of class II major histocompatibility complex (MHC) and CD1 molecules[17,18]. These dendritic cells process the antigens released in the dermis, re-expressing part of them as peptide-MHC complexes on the surface and after they have acquired immune stimulatory capacity, migrate to the para-cortical area of the regional lymph nodes, where they present the antigens to CD8+ and CD4+ T lynphocytes[19,20]. Different signaling pathways are involved in promoting this mechanism, such as increased expression of MHC antigens, interleukin (IL)-1β, IL-6, IL-12 and tumor necrosis factor-α[21]. Furthermore the release of antigens directly in the dermis affects the migration of dendritic cell precursors from the blood stream to the dermis[19,22,23]. CD8+ T cells clonally expand and become effector and memory T cells, while CD4+ T cells promote the differentiation of B cells into antibody producing plasma cells[20]. This route is more immunogenic, due to the direct release of antigens to the skin immune system, compared with intramuscular vaccination that stimulates T-cell response, due to the lack of dendritic cells in muscles. Studies conducted on smallpox, rabies, Bacillus Calmette-Guérin and hepatitis B vaccines supported this hypothesis[24,25].

After the introduction of the Mantoux method[26] and the experience with intradermally administered “typhoid fever” vaccine reported by Tuft *et al*[26], the intradermal route has been investigated in order to evaluate safety and immunogenicity of several vaccines which could be administered by intradermal route. These studies were conducted on vaccination against measles[27,28], cholera[29], rabies[30,31], hepatitis B[32,33] and poliomyelitis[34,35].

Vaccination by intradermal route was used during the smallpox eradication campaign by employing a bifurcated needle to deposit a dose of live vaccine into the skin[36]. In addiction Bacillus Calmette-Guérin vaccination is to date administered by intradermal route using the Mantoux technique, which is based on the injection of a hypodermic needle directly into the skin[37,38].

Since 1991, the World Health Organization has promoted in developing countries the use of the Mantoux method as a less expensive and effective practice for vaccination against rabies[39].

In recent years the administration of influenza vaccine by intradermal route has been introduced in many parts of the world due to its greater immunogenicity compared to vaccination by intramuscular route[40]. In this case, intradermal administration of the vaccine is performed using a micro-needle syringe directly injected into the skin[41].

Moreover economic studies seem to suggest that the cost-savings advantages of administering vaccines by intradermal (ID) route, could be significant[42,43].

In addition the cellular immune response to hepatitis B surface antigen (HBsAg) evocated by ID route can be determined by the appearance of a skin reaction at the injection site, as demonstrated by Leonardi *et al*[44] and Vitaliti *et al*[45]. The development of this reaction on the site of the intradermal injection may represent a cost-savings practice for the Health Organization to test serum anti-HBs response after the booster dose[43].

Recently new devices for intradermal vaccination have been introduced in order to make the skin an effective and safe route for vaccine administration[46].

**ID VACCINATION IN NON RESPONDERS PATIENTS: A REVIEW OF THE LITERATURE**

There are some diseases, like chronic kidney disease,human immunodeficiency virus infection (HIV), chronic liver disease, celiac disease, thalassaemia, type I diabetes mellitus, down’s syndrome and other forms of mental retardation that are characterized by a poor response to HBV vaccination[47-49].

This review focuses on the use of anti hepatitis B vaccine by intradermal route as alternative to conventional intramuscular vaccine in all non responder patients. A comprehensive review of the literature using PubMed database, with appropriate terms, was undertaken for articles in English published since 1983. The literature search was undertaken in September 2013. All studies published on PubMed are reported on Table 1.

***Chronic kidney disease, hemodialysis and renal transplantation***

Patients with advanced chronic kidney disease (CKD) have an impaired immune response to hepatitis B vaccination. In fact even using higher vaccine doses, only 50% to 85% of dialysis patients achieve a protective titer (> 10 IU/L) after hepatitis B vaccination[50-54]. Moreover anti-HBs titer in dialysis patients tends to fall quicker than in healthy subjects[50,55,53].

Numerous genetic and acquired factors are involved in unresponsiveness to hepatitis B vaccination. In the 70-ties of the past century, immune response to HBsAg in HBV infected hemodialysis (HD) patients was linked to HLA[56,57]. In 1990, non responders HD patients had shown to have a higher frequency of HLA-A1, B8 and DR3 than responders[58]. More recently, interleukin genotypes (examples IL10, IL-12, IL-18) were related to the anti-HBs development in response to HBsAg in HD patients[59,60]. Another factor that negatively affect the response to hepatitis B vaccination seems to be an increasing of age[61-63]. Seroconversion rate to anti-HBs positivity after vaccination was 84% in HD patients below 40 years and only 33% in those ≥ 60 years[52]. Moreover poor response to hepatitis B vaccination in dialysis patients has been linked to male gender[58,64], low serum albumin concentration, bad nutritional status[65,66], serological positivity for hepatitis C virus (HCV)[67] or HIV[68], and diabetes mellitus[59,69]. Futhermore vitamin D deficiency could negatively affect antibody formation upon hepatitis B vaccination in stage 3-5D CKD patients[70]. It is well known that dialysis patients have an impaired immune function and there is a positive correlation between increase of immune abnormalities and deterioration of renal function. The best example is correlation of serum soluble CD40 levels with creatinine in non-dialyzed CKD patients. Soluble CD40 is capable to inhibit immunoglobulin production by CD154-activated B lymphocytes in vitro and there is a positive correlation between the serum levels of soluble CD40 and the poor response to hepatitis B vaccination[71]. The decline of the immune system in the course of CKD should represent a valid reason for vaccinating CKD patients in early stages of their renal diseases. According to European Best Practice Guidelines (2002) “patients with progressive renal failure should be vaccinated against HBV preferably before the start on HD”[51] and the United States Center for Disease Control and Prevention suggests to administer three further doses of intramuscular vaccine in hemodialysis patients[55].

For CKD patients who do not respond to six doses of vaccine, there are no evidences about the use of further intramuscular doses. Different strategies have been suggested in order to increase the vaccine-induced seroconversion rate in patients with advanced CKD. In particular the ID vaccination was studied either alone or in combination with conventional intramuscular route.

Hepatitis B vaccination schedule based on the combined use of the intradermal and intramuscular routes, was elaborated in 1994 by Marangi *et al*[72] in CKD patients with serum creatinine concentration ≥ 4 mg/dL and gave very promising effects. The intramuscular dose of 40 micrograms of a DNA-recombinant vaccine was administered to all chronic uremic patients at 0, 1, 2 and 6 mo and two further IM booster dose at 12 and 18 mo in order to achieve an antibody titre > 100 mIU/mL. Moreover intradermal inoculation of 5 micrograms of vaccine every 2 wk was administered for those patients who did not have a protective titre (> or = 10 mIU/mL) even after 19 mo. All patients developed sero-protection.

Another strategy is the administration of HBV vaccination only by intradermal route. In 1997 Fabrizi *et al*[73] conducted a randomized study on 50 chronic dialysis patients who did not develop a sero-conversion rate after a reinforced protocol of hepatitis B vaccine given by IM route. These patients were randomly re-vaccinated by intradermal or intramuscular route. Patients of ID group received 16 doses of 5 μg of HBs antigen weekly, whereas patients of the IM group received two doses of 40 μg of vaccine monthly. One month after the end of re-vaccination protocol, sero-conversion rates and proportion of patients who developed protective anti-HBs titers were significantly higher in ID compared to IM patients (100% *vs* 48% and 96% *vs* 40% respectively). More recently Chanchairujira *et al*[74] revaccinated non responder hemodialysis patients with ID or IM vaccine: 25 patients were treated with 7 doses of 10 μg of HBV vaccine by intradermal route every 2 wk and other 26 patients were treated with 40 μg by intramuscular route at 0, 1, 2 and 6 mo. The Authors found a higher percentage of “responders” in the group of patients who were treated by intradermal administration of the vaccine. At 7 mo after the first vaccination, good (anti HBs titer between 10-999 IU/L) and excellent responders (anti HBs titer > 1000 IU/L) in the ID group were respectively 72% (18/25) and 20% (5/25) compared with 34.5% (9/26) and 34.5% (9/26) of IM group (*P* > 0.05)[74]. In 2009 Barraclough *et al*[75] revaccinated 59 hemodialysis patients non responsive to primary HBV vaccination, with either ID (10 μg of vaccine every week for 8 wk) or IM (40 μg of vaccine at weeks 1 and 8) HBV vaccine. Seroconversion rates to 24 mo, were 79% ID versus 40% IM (*P* = 0.002). Moreover they found a trend toward longer duration of seroprotection with ID vaccination. The authors concluded that ID vaccination should become the standard of care in this population.

Finally a recent meta-analysis conducted by Fabrizi *et al*[76] on 12 controlled trials in order to compare intramuscular *vs* intradermal HBV vaccination in 640 CKD patients, demonstrated that intradermal route provides an higher serocoversion rate than intramuscular route. This result occurred in spite of a lower amount of antigen administered with intradermal route.

***HIV infection***

HBV vaccination has been extensively investigated in patients with HIV infection due to the high prevalence of co-infection. In fact the US HIV Outpatient Study cohort[77], between 1996 and 2007, showed that the prevalence of co-infection with HBV was 20 times higher than in general population (8.4%). In another US study between 1998 and 2001[78], the incidence of hepatitis B infection in patients with HIV, was 370 times higher than in the general population (12.2/1000 persons each year). HIV infection negatively influences different phases of hepatitis B infection, promoting virus replication, the development of chronic infection and the loss of HBs antibody. Furthermore co-infection of hepatitis B and HIV provides an higher incidence of complications, such as hepatocellular carcinoma, cirrhosis and liver-related mortality compared to HIV mono-infection[79,80]. In addition, the probability of developing hepato-toxicity after highly active antiretroviral therapy (HAART) is higher in patients with HIV infection who are also infected by hepatitis B virus[80,81]. For all these reasons individuals with HIV infection should receive vaccine against hepatitis B with the conventional three doses[82-86]. Despite this prophylactic measure, patients with HIV infection develop protective anti-HBs titers in only 18%–71% of cases after three doses of vaccine[87-89]. Individuals with HIV who are non-responders to hepatitis B vaccination, are not protected from infection because they become infected with hepatitis B virus as unvaccinated subjects with HIV[90]. Different factors, such as viral load, CD4 cell count and HAART, can impair the response to hepatitis B vaccination.

Some studies have demonstrated a link between low viral load of HIV and the development of an anti-HBs protective titer for either standard-dose[87,91-94] or double-dose vaccinations[95-98].

B cell dysfunction has been shown in patients with HIV[99,100]. This immunological dysfunction may result in a decreased antibody response among HIV-infected patients[101]. On this regard Mehta *et al*[102] showed a lower number of hepatitis B virus specific memory B cells after vaccination in adolescents with HIV.

On the other hand some studies have suggested that the poor response to HBV vaccination could be attributed to impaired T-cell function[103]. In fact the higher number of T regulatory cells in individuals with HIV is often associated with unresponsiveness to HBV vaccination[104,105]. T regulatory cells inhibit B cell proliferation by inducing their apoptosis[106].

Although HIV-infected patients who do not respond to the conventional three doses may develop a protective immune response after revaccination, they could lose anti HBs titres faster than patients who respond to the first vaccination series, as showed by Cruciani *et al*[107]  and Rey *et al*[90].

In patients with HIV infection, the intradermal route seems to have a greater immunogenicity compared to intramuscular route[108].

In 2011 Launay *et al*[109] performed a randomized study on 437 patients in order to compare the safety and immunogenicity of 4 intramuscular double-dose (40 μg) and 4 intradermal low-dose (4 μg) regimens *vs* the standard hepatitis B vaccine regimen (20 μg × three doses). They found that intradermal vaccine recipients had significantly better sero-conversion rates compared with the standard dose group at week 28 (77% *vs* 65%) but there was no difference between the 4 intramuscular double-dose regimen and the 4 intradermal low-dose regimen.

However intradermal route permit to elicit a better immune response using only 20% of the dose compared to intramuscular route.

In only one pediatric randomized study conducted in order to compare ID vs IM HBV vaccination in children with HIV infection, the percentage of responders to ID route resulted similar to IM route at the end of the third dose of vaccine (90.2% ID *vs* 92.3% IM)[110].

***Chronic liver disease and liver transplantation***

With regard to liver transplantation, a de novo HBV infection increases post-transplant morbidity and mortality[111]. For this reason pre-transplant vaccination represent a valid prophylactic measure, although there are currently few data about the efficacy of HBV vaccination among patients with advanced liver disease[112,113]. On this regard Dhillon S. et al in a recent retrospective review administered HBV vaccination by intradermal route in individuals with chronic liver disease (CLD) who had not developed a protective anti-HBs titer after three doses of 40 μg IM vaccine and booster doses of either 40 or 80 μg IM[114]. 42 patients were treated with a 40 μg ID total dose for a maximum of three doses. 29/42 (69%) subjects developed an anti HBs titer > 10 mIU/mL and 15 (51%) of the responders developed an anti HBs titer > 100 mIU/mL. The authors conclude that high-dose ID HBV vaccination in patients with CLD is efficacious and safe.

***Celiac disease***

Some studies documented that in celiac disease (CD) the immune response to vaccination does not differ from that one found in healthy subjects except for HBV vaccination[12,115]. It has been postulated that HLA-DQ2 haplotype, over-represented in celiac population, could predispose celiac patients to a poorer response to hepatitis B vaccination[116]. On the contrary other studies suggest that in celiac patients gluten consumption could affect the immune response to HBV vaccine[117,118]. Since in celiac patients the interaction between specific deaminated glutamine residues of gliadin and HLA-DQ2 or DQ8 molecules is responsible for the development of intestinal damage[119], it has been postulated that gliadin peptides compete with HBsAg protein fragments for binding to HLA-DQ2 molecules, and this competition could result in an impaired immune response to HBV vaccination in CD[120]. To support this hypothesis recent data of the literature suggest to revaccinate celiac patients during a correct gluten free diet[48,118,121,122]. For this reason new vaccination strategies for non responders celiac patients have been suggested[100,101,106]. In 2010 Leonardi *et al*[123] revaccinated 20 celiac patients who had not responded to HBV vaccination with a 2 μg dose of HBV vaccine by intradermal route. The authors found that after the first booster dose 8/20 patients (40%) developed anti-HBs titer ≥ 1000 mIU/mL, 4/20 (20%) between 100 and 1000 mIU/mL, and 3/20 (15%) between 10 and 99 mIU/mL. Moreover in 2011 the same authors[124] revaccinated 58 non-responder celiac patients with ID (2 μg) or IM vaccine (10 μg) for a maximum of three booster doses, in order to compare the safety and the efficacy of these two different vaccine routes (ID vs IM). The Authors found a similar percentage of “responders” after the third booster dose (ID = 90% *vs* IM = 96.4%), although they documented an higher percentage of patients with an anti-HBs titer > 1000 IU/L in ID (40%) than in IM (7.1%) group.

**OTHER CONDITIONS**

The immune response to hepatitis B vaccination seems to be poorer in patients with insulin dependent diabetes mellitus (IDDM) than in healthy population[125-127]. This seem to depend on genetic factors: in fact HLA-A11, which favors the immune response to hepatitis B vaccination, is present more frequently in responder subjects, while HLA-DR3, DR4, DR7, and B8 have an higher prevalence in patients who respond poorly or do not respond completely as those with diabetes mellitus[128-130]. However there is in literature only one study which evaluated the effectiveness of intradermal route in diabetic patients and compared the immune response to hepatitis B vaccine by intradermal or intramuscular route[131]. All the children enrolled in this trial were divided into four groups: A, B, A1 and B1. 9 children with diabetes mellitus in group A received 3 μg of a recombinant DNA hepatitis B vaccine by intradermal route at 0, 2, 4 and 6 or 8 weeks, while other 9 children affected by diabetes mellitus in group B received three doses of 10 μg (for patients younger than 10 years) or 20 μg (for patients older than 10 years) of the same vaccine by intramuscular route at 0, 1 and 6 months. In addiction 24 normal children of which 12 in group A1 and 12 in B1 received the same vaccine schedule as groups A and B. The authors found that there was a poorer immune response to intradermal hepatitis B vaccine in children with IDDM when compared with controls (*P* < 0.001) and with group B children with IDDM (*P* < 0.001).Recently Fabrizi *et al*[132] conducted a meta-analysis on 12 studies involving 1002 unique patients, in order to assess whether diabetes mellitus could affect the immune response to HBV vaccination in dialysis patients. The authors found a significant decrease in seroconversion rates in patients with diabetes mellitus *vs* non diabetic patients.

Thalassaemic subjects who have been vaccinated against hepatitis B virus often show a loss of anti HBs titer; moreover, between 5% and 20% of subjects who have been immunized against hepatitis B virus do not respond to the hepatitis B vaccine after either conventional or booster vaccination[133,134]. In literature is reported only one study about the use of anti-hepatitis B intradermal route to vaccinate non responder thalassaemic patients[44] . The authors studied 56 children with thalassaemia who had been vaccinated against hepatitis B virus by IM route. In these patients the vaccine was administered in doses of 5 μg by intradermal route and the inoculations were continued every two weeks until the titer had risen above 10 U/L. 45/56 children (80%) with thalassaemia developed HBs antibody titer > 10 U/L two weeks after the first intradermal dose. In other 9 of 11 (82%) non-responding thalassaemic patients the anti- HBs titre was > 10 U/L two weeks after the second intradermal dose. This study showed that low doses of vaccine against hepatitis B virus administered by intradermal route produce an effective immune response in thalassaemic patients.

In addiction there are in literature four studies which investigate the use of intradermal hepatitis B vaccination in patients with Down’s syndrome and other forms of mental retardation (OMR), but the available data are still discordant. In fact two studies suggest that low dose vaccination against hepatitis B by intradermal route, seems to be a suitable cost-reducing immunization system in institutes for mentally retarded patients and its use is safe and effective[135,136]. In another study on follow up the authors concluded that using the intradermal route the antibody response persisted for 2 years in the OMR patients, while decreased remarkably in the DS patients[137]. Only the fourth study concluded that intradermal vaccination is not warranted in persons with DS, especially not in middle aged and older persons[138].

Knowledge of non-response to hepatitis B vaccination is critical also for healthcare workers (HCWs) who are at continuous risk of infection. Around 10%–15% adults do not respond to three doses of anti hepatitis B vaccination or respond poorly[139,140]. Alternative vaccination programs have been studied for non-responders HCWs.

Three studies, have shown that high dose (20 μg) of intradermal vaccine are immunogenic in persons who did not respond to IM vaccination[141,142].

More recently Ghebrehewet *et al*[143] conducted an observational study on 23 non-responding HCWs. All eligible HCWs were vaccinated with two doses of 20 μg of recombinant hepatitis B vaccine intradermally. The authors found that 21/23 (91.3%) of all non-responders developed protective titers (≥ 10 mIU/mL) after 1 or 2 doses of IDRV.

The most recent Cochrane review[144] identified 7 randomized studies that compared the two different routes (ID *vs* IM) evaluating the anti-HBs sero-conversion. The review concluded that the 20 μg vaccine by intramuscular route elicits a better anti-HBs response than the 2 μg vaccine by intradermal route. Despite these results, the authors suggest to further investigate the intradermal route because the doses used by the two routes differ 10 fold while the seroconversion rates differed less than two-fold.

**CONCLUSION**

It is imaginable that within the not too distant future all people in the world will be vaccinated on the mandatory basis. The World Health Organization has recommended that hepatitis B vaccination should be performed for all children in the world and cost-benefit analyses have supported the introduction of universal vaccination against HBV to newborns[145,146]. Results of children’s vaccination, which were evaluated in the six-year outcome of the program, showed neither new cases of HBsAg de novo nor seroconversion to anti-HBc positivity[147].

According to the European Consensus Group on hepatitis B immunity[148] a sustained protection against hepatitis B infection is based on immunological memory. Since antibody memory seems to last for at least 15 years in immune-competent subjects using vaccine by intramuscular route, we might expect that also who respond to intradermal vaccination with an anti-HBs titer ≥ 10 mIU/mL will develop a prolonged protection.

To date anti hepatitis B intradermal vaccination seems to be an effective alternative to intramuscular route in non responder patients. Vaccines administered by intradermal route promote a dendritic-cell-mediated immune response and require lower amount of antigen compared to vaccines administered by intramuscular route that activate a T-cell-mediated response. In addition economic studies seem to suggest that the cost-savings advantages of administering vaccines by intradermal (ID) route, could be significant[42,43]. Moreover the immune response to HBV vaccination can be determined by the appearance of a skin reaction at the injection site[149]. The development of this reaction on the site of the intradermal injection could represent a cost-savings measure for the Health Organization to test serum anti-HBs response after the booster dose[43]. As many literature data suggest that intradermal vaccines improve sero-conversion rates, it would be reasonable to promote this procedure. However further studies should be conducted in particular focusing on: the ideal dose and timing of the ID vaccination schedule; and the sustainability of the immune response achieved and the need of administering further booster doses.

**REFERENCES**

1 **Shepard CW**, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. *Epidemiol Rev* 2006; **28**: 112-125 [PMID: 16754644 DOI: 10.1093/epirev/mxj009]

2 **Sylvan S**. [WHO spearheads global initiative to eradicate hepatitis B]. *Lakartidningen* 2000; **97**: 3738-3740 [PMID: 11016226]

3 **Zanetti AR**, Van Damme P, Shouval D. The global impact of vaccination against hepatitis B: a historical overview. *Vaccine* 2008; **26**: 6266-6273 [PMID: 18848855 DOI: 10.1016/j.vaccine.2008.09.056]

4 **Liao SS**, Li RC, Li H, Yang JY, Zeng XJ, Gong J, Wang SS, Li YP, Zhang KL. Long-term efficacy of plasma-derived hepatitis B vaccine: a 15-year follow-up study among Chinese children. *Vaccine* 1999; **17**: 2661-2666 [PMID: 10418916 DOI: 10.1016/S0264-410X(99)00031-6]

5 **Rendi-Wagner P**, Kundi M, Stemberger H, Wiedermann G, Holzmann H, Hofer M, Wiesinger K, Kollaritsch H. Antibody-response to three recombinant hepatitis B vaccines: comparative evaluation of multicenter travel-clinic based experience. *Vaccine* 2001; **19**: 2055-2060 [PMID: 11228377 DOI: 10.1016/S0264-410X(00)00410-2]

6 **Goldstein ST**, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *Int J Epidemiol* 2005; **34**: 1329-1339 [PMID: 16249217 DOI: 10.1093/ije/dyi206]

7 **Arguedas MR**, McGuire BM, Fallon MB. Implementation of vaccination in patients with cirrhosis. *Dig Dis Sci* 2002; **47**: 384-387 [PMID: 11855555 DOI: 10.1023/A: 1013734525348]

8 **Poland GA**. Evaluating existing recommendations for hepatitis A and B vaccination. *Am J Med* 2005; **118** Suppl 10A: 16S-20S [PMID: 16271536 DOI: 10.1016/j.amjmed.2005.07.029]

9 **Wiedmann M**, Liebert UG, Oesen U, Porst H, Wiese M, Schroeder S, Halm U, Mössner J, Berr F. Decreased immunogenicity of recombinant hepatitis B vaccine in chronic hepatitis C. *Hepatology* 2000; **31**: 230-234 [PMID: 10613751 DOI: 10.1002/hep.510310134]

10 **Keeffe EB**. Acute hepatitis A and B in patients with chronic liver disease: prevention through vaccination. *Am J Med* 2005; **118** Suppl 10A: 21S-27S [PMID: 16271537 DOI: 10.1016]

11 **Yu AS**, Cheung RC, Keeffe EB. Hepatitis B vaccines. *Infect Dis Clin North Am* 2006; **20**: 27-45 [PMID: 16527647 DOI: 10.1016/j.idc.2006.01.004]

12 **Park SD**, Markowitz J, Pettei M, Weinstein T, Sison CP, Swiss SR, Levine J. Failure to respond to hepatitis B vaccine in children with celiac disease. *J Pediatr Gastroenterol Nutr* 2007; **44**: 431-435 [PMID: 17414139 DOI: 10.1097/MPG.0b013e3180320654]

13 **Chen J**, Liang Z, Lu F, Fang X, Liu S, Zeng Y, Zhu F, Chen X, Shen T, Li J, Zhuang H. Toll-like receptors and cytokines/cytokine receptors polymorphisms associate with non-response to hepatitis B vaccine. *Vaccine* 2011; **29**: 706-711 [PMID: 21111021 DOI: 10.1016/]

14 **Hutin YJ**, Hauri AM, Armstrong GL. Use of injections in healthcare settings worldwide, 2000: literature review and regional estimates. *BMJ* 2003; **327**: 1075 [PMID: 14604927 DOI: 10.1136/bmj.327.7423.1075]

15 **Hohlfeld R**, Engel AG. The immunobiology of muscle. *Immunol Today* 1994; **15**: 269-274 [PMID: 8068173 DOI: 10.1016/0167-5699(94)90006-X]

16 **Kupper TS**, Fuhlbrigge RC. Immune surveillance in the skin: mechanisms and clinical consequences. *Nat Rev Immunol* 2004; **4**: 211-222 [PMID: 15039758 DOI: 10.1038/nri1310]

17 **Lenz A**, Heine M, Schuler G, Romani N. Human and murine dermis contain dendritic cells. Isolation by means of a novel method and phenotypical and functional characterization. *J Clin Invest* 1993; **92**: 2587-2596 [PMID: 8254016 DOI: 10.1172/JCI116873]

18 **Spellberg B**. The cutaneous citadel: a holistic view of skin and immunity. *Life Sci* 2000; **67**: 477-502 [PMID: 10993114 DOI: 10.1016/S0024-3205(00)00653-6]

19 **Flacher V**, Bouschbacher M, Verronèse E, Massacrier C, Sisirak V, Berthier-Vergnes O, de Saint-Vis B, Caux C, Dezutter-Dambuyant C, Lebecque S, Valladeau J. Human Langerhans cells express a specific TLR profile and differentially respond to viruses and Gram-positive bacteria. *J Immunol* 2006; **177**: 7959-7967 [PMID: 17114468]

20 **Nicolas JF**, Guy B. Intradermal, epidermal and transcutaneous vaccination: from immunology to clinical practice. *Expert Rev Vaccines* 2008; **7**: 1201-1214 [PMID: 18844594 DOI: 10.1586/14760584.7.8.1201]

21 **Lambert PH**, Laurent PE. Intradermal vaccine delivery: will new delivery systems transform vaccine administration? *Vaccine* 2008; **26**: 3197-3208 [PMID: 18486285 DOI: 10.1016/j.vaccine.2008.03.095]

22 **Le Borgne M**, Etchart N, Goubier A, Lira SA, Sirard JC, van Rooijen N, Caux C, Aït-Yahia S, Vicari A, Kaiserlian D, Dubois B. Dendritic cells rapidly recruited into epithelial tissues via CCR6/CCL20 are responsible for CD8+ T cell crosspriming in vivo. *Immunity* 2006; **24**: 191-201 [PMID: 16473831]

23 **Allan RS**, Waithman J, Bedoui S, Jones CM, Villadangos JA, Zhan Y, Lew AM, Shortman K, Heath WR, Carbone FR. Migratory dendritic cells transfer antigen to a lymph node-resident dendritic cell population for efficient CTL priming. *Immunity* 2006; **25**: 153-162 [PMID: 16860764]

24 **Briggs DJ**, Banzhoff A, Nicolay U, Sirikwin S, Dumavibhat B, Tongswas S, Wasi C. Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine. *Bull World Health Organ* 2000; **78**: 693-698 [PMID: 10859864]

25 **Plotkin SA**. Vaccines: the fourth century. *Clin Vaccine Immunol* 2009; **16**: 1709-1719 [PMID: 19793898 DOI: 10.1128/CVI.00290-09]

26 **Icardi G**, Orsi A, Ceravolo A, Ansaldi F. Current evidence on intradermal influenza vaccines administered by Soluvia™ licensed micro injection system. *Hum Vaccin Immunother* 2012; **8**: 67-75 [PMID: 22293531]

27 . Comparative trial of live attenuated measles vaccine in Hong Kong by intramuscular and intradermal injection. *Bull World Health Organ* 1967; **36**: 375-384 [PMID: 5299670]

28 **Cutts FT**, Clements CJ, Bennett JV. Alternative routes of measles immunization: a review. *Biologicals* 1997; **25**: 323-338 [PMID: 9325001 DOI: 10.1006/biol.1997.0103]

29 **McBean AM**, Agle AN, Compaore P, Foster SO, McCormack WM. Comparison of intradermal and subcutaneous routes of cholera vaccine administration. *Lancet* 1972; **1**: 527-529 [PMID: 4110029 DOI: 10.1016/S0140-6736(72)90187]

30 **Nicholson KG**, Prestage H, Cole PJ, Turner GS, Bauer SP. Multisite intradermal antirabies vaccination. Immune responses in man and protection of rabbits against death from street virus by postexposure administration of human diploid-cell-strain rabies vaccine. *Lancet* 1981; **2**: 915-918 [PMID: 6117693]

31 **Warrell MJ**, Nicholson KG, Warrell DA, Suntharasamai P, Chanthavanich P, Viravan C, Sinhaseni A, Chiewbambroongkiat MK, Pouradier-Duteil X, Xueref C. Economical multiple-site intradermal immunisation with human diploid-cell-strain vaccine is effective for post-exposure rabies prophylaxis. *Lancet* 1985; **1**: 1059-1062 [PMID: 2860284 DOI: 10.1016/S0140-6736(85)92367-0]

32 **Miller KD**, Gibbs RD, Mulligan MM, Nutman TB, Francis DP. Intradermal hepatitis B virus vaccine: immunogenicity and side-effects in adults. *Lancet* 1983; **2**: 1454-1456 [PMID: 6140546 DOI: 10.1016/S0140-6736(83)90800-0]

33 **Clarke JA**, Hollinger FB, Lewis E, Russell LA, Miller CH, Huntley A, Flynn NM. Intradermal inoculation with Heptavax-B. Immune response and histologic evaluation of injection sites. *JAMA* 1989; **262**: 2567-2571 [PMID: 2530364 DOI: 10.1001/jama.262.18.2567]

34 **Connolly JH**, Dick GW. Antibody response following intradermal or oral administration of formalinised poliomyelitis. *Lancet* 1958; **2**: 333-336 [PMID: 13576796 DOI: 10.1016/S0140-6736(58)90256-3]

35 **Nirmal S**, Cherian T, Samuel BU, Rajasingh J, Raghupathy P, John TJ. Immune response of infants to fractional doses of intradermally administered inactivated poliovirus vaccine. *Vaccine* ; **16**: 928-931 [PMID: 9682339 DOI: 10.1016/S0264-410X(97)00293-4]

36 **Baxby D**. Smallpox vaccination techniques; from knives and forks to needles and pins. *Vaccine* 2002; **20**: 2140-2149 [PMID: 11972983 DOI: 10.1016/S0264-410X(02)00028-2]

37 **Andersen P**, Doherty TM. The success and failure of BCG - implications for a novel tuberculosis vaccine. *Nat Rev Microbiol* 2005; **3**: 656-662 [PMID: 16012514 DOI: 10.1038/nrmicro1211]

38 **Flynn PM**, Shenep JL, Mao L, Crawford R, Williams BF, Williams BG. Influence of needle gauge in Mantoux skin testing. *Chest* 1994; **106**: 1463-1465 [PMID: 7956403 DOI: 10.1378/chest.106.5.1463]

39 **WHO**. Rabies vaccines. WHO position paper. *Wkly Epidemiol Rec* 2007; **82**: 425-435 [PMID: 18064757]

40 **Arnou R**, Icardi G, De Decker M, Ambrozaitis A, Kazek MP, Weber F, Van Damme P. Intradermal influenza vaccine for older adults: a randomized controlled multicenter phase III study. *Vaccine* 2009; **27**: 7304-7312 [PMID: 19849996 DOI: 10.1016/j.vaccine.2009.10.033]

41 **Laurent PE**, Bonnet S, Alchas P, Regolini P, Mikszta JA, Pettis R, Harvey NG. Evaluation of the clinical performance of a new intradermal vaccine administration technique and associated delivery system. *Vaccine* 2007; **25**: 8833-8842 [PMID: 18023942]

42 **Sangaré L**, Manhart L, Zehrung D, Wang CC. Intradermal hepatitis B vaccination: a systematic review and meta-analysis. *Vaccine* 2009; **27**: 1777-1786 [PMID: 19200451 DOI: 10.1016/j.vaccine.2009.01.043]

43 **Sangfelt P**, Uhnoo I, Reichard O, Weiland O. A low-dose intradermal hepatitis B vaccine programme in health-care workers and students is highly effective and cost saving: a retrospective follow-up survey in the clinical setting. *Scand J Gastroenterol* 2008; **43**: 465-472 [PMID: 18365912 DOI: 10.1080/00365520701733806]

44 **Leonardi S**, Leggio T, Sciacca A, Di Gregorio F, Musumeci S. Intradermal hepatitis B vaccination in thalassaemia. *Arch Dis Child* 1990; **65**: 527-529 [PMID: 2141464 DOI: 10.1136/adc.65.5.527]

45 **Vitaliti G**, Praticò AD, Cimino C, Di Dio G, Lionetti E, La Rosa M, Leonardi S. Hepatitis B vaccine in celiac disease: yesterday, today and tomorrow. *World J Gastroenterol* 2013; **19**: 838-845 [PMID: 23430309 DOI: 10.3748/wjg.v19.i6.838]

46 **Kim YC**, Prausnitz MR. Enabling skin vaccination using new delivery technologies. *Drug Deliv Transl Res* 2011; **1**: 7-12 [PMID: 21799951]

47 **Degos F**, Duhamel G, Brechot C, Nalpas B, Courouce AM, Tron F, Berthelot P. Hepatitis B vaccination in chronic alcoholics. *J Hepatol* 1986; **2**: 402-409 [PMID: 2941477 DOI: 10.1016/S0168-8278(86)80051-4]

48 **Ertekin V**, Tosun MS, Selimoglu MA. Is there need for a new hepatitıs B vaccine schedule for children with celiac disease? *Hepat Mon* 2011; **11**: 634-637 [PMID: 22140387 DOI: 10.5812/kowsar.1735143X.715]

49 **Niiya T**, Akbar SM, Yoshida O, Miyake T, Matsuura B, Murakami H, Abe M, Hiasa Y, Onji M. Impaired dendritic cell function resulting from chronic undernutrition disrupts the antigen-specific immune response in mice. *J Nutr* 2007; **137**: 671-675 [PMID: 17311958]

50 **Shakhgil'dian IV**, Khukhlovich PA, Savin EA, Kuzin SN, Anan'ev VA, Sergeeva NA, Khasanova VA, Shostka GD, Vu Z, Vasil'ev AN. [Risk of infection with hepatitis B and C viruses of medical workers, patients in the hemodialysis ward, and vaccine prophylaxis of hepatitis B infection in these populations]. *Vopr Virusol* 1994; **39**: 226-229 [PMID: 7716909]

51 **European Best Practice Guidelines**. Prevention and management of HBV, HCV and HIV in HD patients. *Nephrol Dial Transpl*2002; **17**: 72-87

52 **Fabrizi F**, Dixit V, Bunnapradist S, Martin P. Meta-analysis: the dialysis mode and immunological response to hepatitis B virus vaccine in dialysis population. *Aliment Pharmacol Ther* 2006; **23**: 1105-1112 [PMID: 16611270 DOI: 10.1111/j.1365-2036.2006.02877.x]

53 **Tsouchnikas I**, Dounousi E, Xanthopoulou K, Papakonstantinou S, Thomoglou V, Tsakiris D. Loss of hepatitis B immunity in hemodialysis patients acquired either naturally or after vaccination. *Clin Nephrol* 2007; **68**: 228-234 [PMID: 17969490 DOI: 10.5414/CNP68228]

54 **Centers for Disease Control and Prevention (CDC)**. Infection control requirements for dialysis facilities and clarification regarding guidance on parenteral medication vials. *MMWR Morb Mortal Wkly Rep* 2008; **57**: 875-876 [PMID: 18701878]

55 **Roznovský L**, Tvrdík J, Kabieszová L, Petrousová L, Orságová I, Hozáková L, Lochman I, Kloudová A, Valkovský I, Letocha P, Schwarzová S, Hladík M, Zjevíková A. [Vaccination against hepatitis B in patients with chronic renal failure--twenty years follow-up]. *Vnitr Lek* 2011; **57**: 808-814 [PMID: 22097688]

56 **Sengar DP**, McLeish WA, Sutherland M, Couture RA, Rashid A. Hepatitis B antigen (HBAg) infection in a hemodialysis unit. I. HL-A8 and immune response to HBAg. *Can Med Assoc J* 1975; **112**: 968, 971 [PMID: 1093659]

57 **Sengar DP**, Rashid A, Jindal SL, Christie CJ. HLA antigens in HBsAg infection. *Vox Sang* 1979; **36**: 353-355 [PMID: 494572]

58 **Pol S**, Legendre C, Mattlinger B, Berthelot P, Kreis H. Genetic basis of nonresponse to hepatitis B vaccine in hemodialyzed patients. *J Hepatol* 1990; **11**: 385-387 [PMID: 2290031 DOI: 10.1016/0168-8278(90)90226-H]

59 **Girndt M**, Sester U, Sester M, Deman E, Ulrich C, Kaul H, Köhler H. The interleukin-10 promoter genotype determines clinical immune function in hemodialysis patients. *Kidney Int* 2001; **60**: 2385-2391 [PMID: 11737614 DOI: 10.1046/j.1523-1755.2001.00062.x]

60 **Grzegorzewska AE**, Wobszal PM, Mostowska A, Jagodziński PP. Antibodies to hepatitis B virus surface antigen and interleukin 12 and interleukin 18 gene polymorphisms in hemodialysis patients. *BMC Nephrol* 2012; **13**: 75 [PMID: 22863216 DOI: 10.1186/1471-2369-13-75]

61 **Grzegorzewska AE**, Wobszal P, Jagodziński PP. Interleukin-18 promoter polymorphism and development of antibodies to surface antigen of hepatitis B virus in hemodialysis patients. *Kidney Blood Press Res* 2012; **35**: 1-8 [PMID: 21832842 DOI: 10.1159/000329932]

62 **Fabrizi F**, Martin P, Dixit V, Bunnapradist S, Dulai G. Meta-analysis: the effect of age on immunological response to hepatitis B vaccine in end-stage renal disease. *Aliment Pharmacol Ther* 2004; **20**: 1053-1062 [PMID: 15569107 DOI: 10.1111/j.1365-2036.2004.02264.x]

63 **Shatat HZ**, Kotkat AM, Farghaly AG. Immune response to hepatitis B vaccine in haemodialysis patients. *J Egypt Public Health Assoc* 2000; **75**: 257-275 [PMID: 17216922]

64 **Stevens CE**, Alter HJ, Taylor PE, Zang EA, Harley EJ, Szmuness W. Hepatitis B vaccine in patients receiving hemodialysis. Immunogenicity and efficacy. *N Engl J Med* 1984; **311**: 496-501 [PMID: 6235453 DOI: 10.1056/NEJM198408233110803]

65 **Brown CM**, Donlon S, O'Kelly P, Casey AM, Collier C, Conlon PJ, Walshe JJ. A prospective study of hepatitis B vaccination - a comparison of responders versus nonresponders. *Ren Fail* 2011; **33**: 276-279 [PMID: 21401350 DOI: 10.3109/0886022X.2011.559300]

66 **Fernández E**, Betriu MA, Gómez R, Montoliu J. Response to the hepatitis B virus vaccine in haemodialysis patients: influence of malnutrition and its importance as a risk factor for morbidity and mortality. *Nephrol Dial Transplant* 1996; **11**: 1559-1563 [PMID: 8856211 DOI: 10.1093/oxfordjournals.ndt.a027613]

67 **Navarro JF**, Teruel JL, Mateos ML, Marcen R, Ortuno J. Antibody level after hepatitis B vaccination in hemodialysis patients: influence of hepatitis C virus infection. *Am J Nephrol* 1996; **16**: 95-97 [PMID: 8919223 DOI: 10.1159/000168977]

68 **Ahuja TS**, Kumar S, Mansoury H, Rodriguez H, Kuo YF. Hepatitis B vaccination in human immunodeficiency virus-infected adults receiving hemodialysis. *Kidney Int* 2005; **67**: 1136-1141 [PMID: 15698455 DOI: 10.1111/j.1523-1755.2005.00180.x]

69 **Alavian SM**, Tabatabaei SV. The effect of diabetes mellitus on immunological response to hepatitis B virus vaccine in individuals with chronic kidney disease: A meta-analysis of current literature. *Vaccine* 2010; **28**: 3773-3777 [PMID: 20371390]

70 **Zitt E**, Sprenger-Mahr H, Knoll F, Neyer U, Lhotta K. Vitamin D deficiency is associated with poor response to active hepatitis B immunisation in patients with chronic kidney disease. *Vaccine* 2012; **30**: 931-935 [PMID: 22142584 DOI: 10.1016/j.vaccine.2011.11.086]

71 **Contin C**, Pitard V, Delmas Y, Pelletier N, Defrance T, Moreau JF, Merville P, Déchanet-Merville J. Potential role of soluble CD40 in the humoral immune response impairment of uraemic patients. *Immunology* 2003; **110**: 131-140 [PMID: 12941150 DOI: 10.1046/j.1365-2567.2003.01716.x]

72 **Marangi AL**, Giordano R, Montanaro A, De Padova F, Schiavone MG, Dongiovanni G, Basile C. Hepatitis B virus infection in chronic uremia: long-term follow-up of a two-step integrated protocol of vaccination. *Am J Kidney Dis* 1994; **23**: 537-542 [PMID: 815448982]

73 **Fabrizi F**, Andrulli S, Bacchini G, Corti M, Locatelli F. Intradermal versus intramuscular hepatitis b re-vaccination in non-responsive chronic dialysis patients: a prospective randomized study with cost-effectiveness evaluation. *Nephrol Dial Transplant* 1997; **12**: 1204-1211 [PMID: 9198052 DOI: 10.1093/ndt/12.6.1204]

74 **Chanchairujira T**, Chantaphakul N, Thanwandee T, Ong-Ajyooth L. Efficacy of intradermal hepatitis B vaccination compared to intramuscular vaccination in hemodialysis patients. *J Med Assoc Thai* 2006; **89 Suppl 2**: S33-S40 [PMID: 17044452]

75 **Barraclough KA**, Wiggins KJ, Hawley CM, van Eps CL, Mudge DW, Johnson DW, Whitby M, Carpenter S, Playford EG. Intradermal versus intramuscular hepatitis B vaccination in hemodialysis patients: a prospective open-label randomized controlled trial in nonresponders to primary vaccination. *Am J Kidney Dis* 2009; **54**: 95-103 [PMID: 19481320]

76 **Fabrizi F**, Dixit V, Magnini M, Elli A, Martin P. Meta-analysis: intradermal vs. intramuscular vaccination against hepatitis B virus in patients with chronic kidney disease. *Aliment Pharmacol Ther* 2006; **24**: 497-506 [PMID: 16886915 DOI: 10.1111/j.1365-2036.2006.03002.x]

77 **Spradling PR**, Richardson JT, Buchacz K, Moorman AC, Brooks JT. Prevalence of chronic hepatitis B virus infection among patients in the HIV Outpatient Study, 1996-2007. *J Viral Hepat* 2010; **17**: 879-886 [PMID: 20158604 DOI: 10.1111/j.1365-2893.2009.01249.x]

78 **Kellerman SE**, Hanson DL, McNaghten AD, Fleming PL. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. *J Infect Dis* 2003; **188**: 571-577 [PMID: 12898445 DOI: 10.1086/377135]

79 **Thio CL**, Seaberg EC, Skolasky R, Phair J, Visscher B, Muñoz A, Thomas DL. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002; **360**: 1921-1926 [PMID: 12493258 DOI: 10.1016/S0140-6736(02)11913-1]

80 **Puoti M**, Airoldi M, Bruno R, Zanini B, Spinetti A, Pezzoli C, Patroni A, Castelli F, Sacchi P, Filice G, Carosi G. Hepatitis B virus co-infection in human immunodeficiency virus-infected subjects. *AIDS Rev* 2002; **4**: 27-35 [PMID: 11998781]

81 **Sulkowski MS**, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA* 2000; **283**: 74-80 [PMID: 10632283 DOI: 10.1001/jama.283.1.74]

82 **Kaplan JE**, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009; **58**: 1-207; quiz CE1-4 [PMID: 19357635]

83 **Paitoonpong L**, Suankratay C. Immunological response to hepatitis B vaccination in patients with AIDS and virological response to highly active antiretroviral therapy. *Scand J Infect Dis* 2008; **40**: 54-58 [PMID: 17852939 DOI: 10.1080/00365540701522975]

84 **Mast EE**, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, Rodewald LE, Douglas JM, Janssen RS, Ward JW. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep* 2006; **55**: 1-33; quiz CE1-4 [PMID: 17159833]

85 **Rockstroh JK**, Bhagani S, Benhamou Y, Bruno R, Mauss S, Peters L, Puoti M, Soriano V, Tural C. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med* 2008; **9**: 82-88 [PMID: 18257771 DOI: 10.1111/j.1468-1293.2007.00535.x]

86 **European AIDS Clinical Society**. Guidelines Version 6 – October 2011. Available from: URL: http://europeanaidsclinicalsociety.org/images/stories/EACSPdf/EACSGuidelines-v6.0-English.pdf

87 **Geretti AM**, Brook G, Cameron C, Chadwick D, Heyderman RS, MacMahon E, Pozniak A, Ramsay M, Schuhwerk M. British HIV Association guidelines for immunization of HIV-infected adults 2008. *HIV Med* 2008; **9**: 795-848 [PMID: 18983477 DOI: 10.1111/j.1468-1293.2008.00637.x]

88 **Tedaldi EM**, Baker RK, Moorman AC, Wood KC, Fuhrer J, McCabe RE, Holmberg SD. Hepatitis A and B vaccination practices for ambulatory patients infected with HIV. *Clin Infect Dis* 2004; **38**: 1478-1484 [PMID: 15156488 DOI: 10.1086/420740]

89 **Rey D**, Krantz V, Partisani M, Schmitt MP, Meyer P, Libbrecht E, Wendling MJ, Vetter D, Nicolle M, Kempf-Durepaire G, Lang JM. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects on HIV-1 viral load. *Vaccine* 2000; **18**: 1161-1165 [PMID: 10649616 DOI: 10.1016/S0264-410X(99)00389-8]

90 **Hadler SC**, Judson FN, O'Malley PM, Altman NL, Penley K, Buchbinder S, Schable CA, Coleman PJ, Ostrow DN, Francis DP. Outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. *J Infect Dis* 1991; **163**: 454-459 [PMID: 1825315 DOI: 10.1093/infdis/163.3.454]

91 **Overton ET**, Sungkanuparph S, Powderly WG, Seyfried W, Groger RK, Aberg JA. Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons. *Clin Infect Dis* 2005; **41**: 1045-1048 [PMID: 16142673 DOI: 10.1086/433180]

92 **Kim HN**, Harrington RD, Van Rompaey SE, Kitahata MM. Independent clinical predictors of impaired response to hepatitis B vaccination in HIV-infected persons. *Int J STD AIDS* 2008; **19**: 600-604 [PMID: 18725550 DOI: 10.1258/ijsa.2007.007197]

93 **Bailey CL**, Smith V, Sands M. Hepatitis B vaccine: a seven-year study of adherence to the immunization guidelines and efficacy in HIV-1-positive adults. *Int J Infect Dis* 2008; **12**: e77-e83 [PMID: 18723381 DOI: 10.1016/j.ijid.2008.05.1226]

94 **de Vries-Sluijs TE**, Hansen BE, van Doornum GJ, Kauffmann RH, Leyten EM, Mudrikova T, Brinkman K, den Hollander JG, Kroon FP, Janssen HL, van der Ende ME, de Man RA. A randomized controlled study of accelerated versus standard hepatitis B vaccination in HIV-positive patients. *J Infect Dis* 2011; **203**: 984-991 [PMID: 21266513 DOI: 10.1093/infdis/jiq137]

95 **Cruciani M**, Mengoli C, Serpelloni G, Lanza A, Gomma M, Nardi S, Rimondo C, Bricolo F, Consolaro S, Trevisan M, Bosco O. Serologic response to hepatitis B vaccine with high dose and increasing number of injections in HIV infected adult patients. *Vaccine* 2009; **27**: 17-22 [PMID: 18984022 DOI: 10.1016/j.vaccine.2008.10.040]

96 **Fonseca MO**, Pang LW, de Paula Cavalheiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine* 2005; **23**: 2902-2908 [PMID: 15780739 DOI: 10.1016/j.vaccine.2004.11.057]

97 **Veiga AP**, Casseb J, Duarte AJ. Humoral response to hepatitis B vaccination and its relationship with T CD45RA+ (naïve) and CD45RO+ (memory) subsets in HIV-1-infected subjects. *Vaccine* 2006; **24**: 7124-7128 [PMID: 16884833 DOI: 10.1016/j.vaccine.2006.06.079]

98 **Potsch DV**, Camacho LA, Tuboi S, Villar LM, Miguel JC, Ginuíno C, Silva EF, Mendonça RM, Moreira RB, Barroso PF. Vaccination against hepatitis B with 4-double doses increases response rates and antibodies titers in HIV-infected adults. *Vaccine* 2012; **30**: 5973-5977 [PMID: 22828589 DOI: 10.1016/j.vaccine.2012.07.028]

99 **Moir S**, Fauci AS. B cells in HIV infection and disease. *Nat Rev Immunol* 2009; **9**: 235-245 [PMID: 19319142 DOI: 10.1038/nri2524]

100 **Moir S**, Buckner CM, Ho J, Wang W, Chen J, Waldner AJ, Posada JG, Kardava L, O'Shea MA, Kottilil S, Chun TW, Proschan MA, Fauci AS. B cells in early and chronic HIV infection: evidence for preservation of immune function associated with early initiation of antiretroviral therapy. *Blood* 2010; **116**: 5571-5579 [PMID: 20837780 DOI: 10.1182/blood-2010-05-285528]

101 **Titanji K**, De Milito A, Cagigi A, Thorstensson R, Grützmeier S, Atlas A, Hejdeman B, Kroon FP, Lopalco L, Nilsson A, Chiodi F. Loss of memory B cells impairs maintenance of long-term serologic memory during HIV-1 infection. *Blood* 2006; **108**: 1580-1587 [PMID: 16645169 DOI: 10.1182/blood-2005-11-013383]

102 **Mehta N**, Cunningham CK, Flynn P, Pepe J, Obaro S, Kapogiannis BG, Bethel J, Luzuriaga K. Impaired generation of hepatitis B virus-specific memory B cells in HIV infected individuals following vaccination. *Vaccine* 2010; **28**: 3672-3678 [PMID: 20356567 DOI: 10.1016/j.vaccine.2010.03.022]

103 **Goncalves L**, Albarran B, Salmen S, Borges L, Fields H, Montes H, Soyano A, Diaz Y, Berrueta L. The nonresponse to hepatitis B vaccination is associated with impaired lymphocyte activation. *Virology* 2004; **326**: 20-28 [PMID: 15262491 DOI: 10.1016/j.virol.2004.04.042]

104 **Bi X**, Suzuki Y, Gatanaga H, Oka S. High frequency and proliferation of CD4+ FOXP3+ Treg in HIV-1-infected patients with low CD4 counts. *Eur J Immunol* 2009; **39**: 301-309 [PMID: 19089812 DOI: 10.1002/eji.200838667]

105 **del Pozo Balado Mdel M**, Leal M, Méndez Lagares G, Mata RC, López-Cortés LF, Viciana P, Pacheco YM. Increased regulatory T cell counts in HIV-infected nonresponders to hepatitis B virus vaccine. *J Infect Dis* 2010; **202**: 362-369 [PMID: 20560766 DOI: 10.1086/653707]

106 **Zhao DM**, Thornton AM, DiPaolo RJ, Shevach EM. Activated CD4+CD25+ T cells selectively kill B lymphocytes. *Blood* 2006; **107**: 3925-3932 [PMID: 16418326]

107 **Kalinowska-Nowak A**, Bociaga-Jasik M, Garlicki A, Mach T. [Efficacy of vaccination against hepatitis B in adult with HIV infection]. *Przegl Epidemiol* 2007; **61**: 339-347 [PMID: 17956052]

108 **Whitaker JA**, Rouphael NG, Edupuganti S, Lai L, Mulligan MJ. Strategies to increase responsiveness to hepatitis B vaccination in adults with HIV-1. *Lancet Infect Dis* 2012; **12**: 966-976 [PMID: 23174382]

109 **Launay O**, van der Vliet D, Rosenberg AR, Michel ML, Piroth L, Rey D, Colin de Verdière N, Slama L, Martin K, Lortholary O, Carrat F. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. *JAMA* 2011; **305**: 1432-1440 [PMID: 21486976 DOI: 10.1001/jama.2011.351]

110 **Bunupuradah T**, Ananworanich J, Pancharoen C, Petoumenos K, Prasitsuebsai W, Wongngam W, Ubolyam S, Sriheara C, Lange J, Phanuphak P, Puthanakit T. Randomized study of intradermal compared to intramuscular hepatitis B vaccination in HIV-infected children without severe immunosuppression. *Vaccine* 2011; **29**: 2962-2967 [PMID: 21329776 DOI: 10.1016/j.vaccine.2011.01.114]

111 **Aziz A**, Aziz S, Li DS, Murphy L, Leone N, Kennedy M, Dhillon S, Van Thiel DH. Efficacy of repeated high-dose hepatitis B vaccine (80 microg) in patients with chronic liver disease. *J Viral Hepat* 2006; **13**: 217-221 [PMID: 16611186 DOI: 10.1111/j.1365-2893.2005.00674.x]

112 **Engler SH**, Sauer PW, Golling M, Klar EA, Benz C, Stremmel W, Kallinowski B. Immunogenicity of two accelerated hepatitis B vaccination protocols in liver transplant candidates. *Eur J Gastroenterol Hepatol* 2001; **13**: 363-367 [PMID: 11338063 DOI: 10.1097/00042737-200104000-00010]

113 **Castells L**, Esteban R. Hepatitis B vaccination in liver transplant candidates. *Eur J Gastroenterol Hepatol* 2001; **13**: 359-361 [PMID: 11338062 DOI: 10.1097/00042737-200104000-00009]

114 **Dhillon S**, Moore C, Li SD, Aziz A, Kakar A, Dosanjh A, Beesla A, Murphy L, Van Thiel DH. Efficacy of high-dose intra-dermal hepatitis B virus vaccine in previous vaccination non-responders with chronic liver disease. *Dig Dis Sci* 2012; **57**: 215-220 [PMID: 22160636 DOI: 10.1007/s10620-011-1996-0]

115 **Leonardi S**, Longo R, Cotugno M, Tardino L, Spina M, Lionetti E, La Rosa M. [Vaccination and celiac disease: results of a retrospective study]. *Minerva Pediatr* 2011; **63**: 363-367 [PMID: 21946447]

116 **Noh KW**, Poland GA, Murray JA. Hepatitis B vaccine nonresponse and celiac disease. *Am J Gastroenterol* 2003; **98**: 2289-2292 [PMID: 14572581 DOI: 10.1111/j.1572-0241.2003.07701.x]

117 **Nemes E**, Lefler E, Szegedi L, Kapitány A, Kovács JB, Balogh M, Szabados K, Tumpek J, Sipka S, Korponay-Szabó IR. Gluten intake interferes with the humoral immune response to recombinant hepatitis B vaccine in patients with celiac disease. *Pediatrics* 2008; **121**: e1570-e1576 [PMID: 18519462 DOI: 10.1542/peds.2007-2446]

118 **Zingone F**, Morisco F, Zanetti A, Romanò L, Portella G, Capone P, Andreozzi P, Tortora R, Ciacci C. Long-term antibody persistence and immune memory to hepatitis B virus in adult celiac patients vaccinated as adolescents. *Vaccine* 2011; **29**: 1005-1008 [PMID: 21129395 DOI: 10.1016/j.vaccine.2010.11.060]

119 **Gasbarrini G**, Miele L, Malandrino N, Grieco A, Addolorato G, Gasbarrini A, Cammarota G, Bonvicini F. Celiac disease in the 21st century: issues of under- and over-diagnosis. *Int J Immunopathol Pharmacol* 2009; **22**: 1-7 [PMID: 19309546]

120 **van Heel DA**, West J. Recent advances in coeliac disease. *Gut* 2006; **55**: 1037-1046 [PMID: 16766754 DOI: 10.1136/gut.2005.075119]

121 **Ertem D**, Gonen I, Tanidir C, Ugras M, Yildiz A, Pehlivanoğlu E, Eksioglu-Demiralp E. The response to hepatitis B vaccine: does it differ in celiac disease? *Eur J Gastroenterol Hepatol* 2010; **22**: 787-793 [PMID: 19584738 DOI: 10.1097/MEG.0b013e32832e9d41]

122 **Leonardi S**, Spina M, Spicuzza L, Rotolo N, La Rosa M. Hepatitis B vaccination failure in celiac disease: is there a need to reassess current immunization strategies? *Vaccine* 2009; **27**: 6030-6033 [PMID: 19682619 DOI: 10.1016/j.vaccine.2009.07.099]

123 **Leonardi S**, Del Giudice MM, Spicuzza L, Spina M, La Rosa M. Hepatitis B vaccine administered by intradermal route in patients with celiac disease unresponsive to the intramuscular vaccination schedule: a pilot study. *Am J Gastroenterol* 2010; **105**: 2117-2119 [PMID: 20818367 DOI: 10.1038/ajg.2010.195]

124 **Leonardi S**, Praticò AD, Lionetti E, Spina M, Vitaliti G, La Rosa M. Intramuscular vs intradermal route for hepatitis B booster vaccine in celiac children. *World J Gastroenterol* 2012; **18**: 5729-5733 [PMID: 23155313 DOI: 10.3748/wjg.v18.i40.5729]

125 **Pozzilli P**, Arduini P, Visalli N, Sutherland J, Pezzella M, Galli C, Corradini SG, Biasio L, Gale EA, Andreani D. Reduced protection against hepatitis B virus following vaccination in patients with type 1 (insulin-dependent) diabetes. *Diabetologia* 1987; **30**: 817-819 [PMID: 2962892 DOI: 10.1007/BF00275749]

126 **Fiçicioğlu C**, Mikla S, Midilli K, Aydin A, Cam H, Erğin S. Reduced immune response to hepatitis B vaccine in children with insulin dependent diabetes. *Acta Paediatr Jpn* 1995; **37**: 687-690 [PMID: 8775551 DOI: 10.1111/j.1442-200X.1995.tb03404.x]

127 **Leonardi S**, Vitaliti G, Garozzo MT, Miraglia del Giudice M, Marseglia G, La Rosa M. Hepatitis B vaccination failure in children with diabetes mellitus? The debate continues. *Hum Vaccin Immunother* 2012; **8**: 448-452 [PMID: 22370513 DOI: 10.4161/hv.19107]

128 **Craven DE**, Awdeh ZL, Kunches LM, Yunis EJ, Dienstag JL, Werner BG, Polk BF, Syndman DR, Platt R, Crumpacker CS. Nonresponsiveness to hepatitis B vaccine in health care workers. Results of revaccination and genetic typings. *Ann Intern Med* 1986; **105**: 356-360 [PMID: 2943202 DOI: 10.7326/0003-4819-105-3-356]

129 **Martinetti M**, De Silvestri A, Belloni C, Pasi A, Tinelli C, Pistorio A, Salvaneschi L, Rondini G, Avanzini MA, Cuccia M. Humoral response to recombinant hepatitis B virus vaccine at birth: role of HLA and beyond. *Clin Immunol* 2000; **97**: 234-240 [PMID: 11112362 DOI: 10.1006/clim.2000.4933]

130 **Egea E**, Iglesias A, Salazar M, Morimoto C, Kruskall MS, Awdeh Z, Schlossman SF, Alper CA, Yunis EJ. The cellular basis for lack of antibody response to hepatitis B vaccine in humans. *J Exp Med* 1991; **173**: 531-538 [PMID: 1825504 DOI: 10.1084/jem.173.3.531]

131 **Li Volti S**, Caruso-Nicoletti M, Biazzo F, Sciacca A, Mandarà G, Mancuso M, Mollica F. Hyporesponsiveness to intradermal administration of hepatitis B vaccine in insulin dependent diabetes mellitus. *Arch Dis Child* 1998; **78**: 54-57 [PMID: 9534677 DOI: 10.1136/adc.78.1.54]

132 **Fabrizi F**, Dixit V, Martin P, Messa P. Meta-analysis: the impact of diabetes mellitus on the immunological response to hepatitis B virus vaccine in dialysis patients. *Aliment Pharmacol Ther* 2011; **33**: 815-821 [PMID: 21281319 DOI: 10.1111/j.1365-2036.2011.04589.x]

133 **Szmuness W**, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): a final report. *Hepatology* ; **1**: 377-385 [PMID: 7030902 DOI: 10.1002/hep.1840010502]

134 **Hadler SC**, Francis DP, Maynard JE, Thompson SE, Judson FN, Echenberg DF, Ostrow DG, O'Malley PM, Penley KA, Altman NL. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *N Engl J Med* 1986; **315**: 209-214 [PMID: 2941687 DOI: 10.1056/NEJM198607243150401]

135 **Hayashi J**, Noguchi A, Nakashima K, Morofuji M, Kashiwagi S. Long term observation of the effect of intradermal hepatitis B vaccination on mentally retarded patients. *Eur J Epidemiol* 1991; **7**: 649-653 [PMID: 1838338]

136 **Heijtink RA**, Breukers AA, den Hartigh G, Schepman RW, Schmitz PI, Schalm SW, Masurel N. Low dose intradermal vaccination against hepatitis B in mentally retarded patients. *Vaccine* 1988; **6**: 59-61 [PMID: 2965462 DOI: 10.1016/0264-410X(88)90016-3]

137 **Van Damme P**, Vranckx R, Meheus A. Immunogenicity of a recombinant DNA hepatitis B vaccine in institutionalized patients with Down's syndrome. *Vaccine* 1990; **8** Suppl: S53-S5; discussion S53-S5 [PMID: 2139285]

138 **Ahman L**, Bäck E, Bensch K, Olcén P. Non-efficacy of low-dose intradermal vaccination against hepatitis B in Down's syndrome. *Scand J Infect Dis* 1993; **25**: 16-23 [PMID: 8460344 DOI: 10.3109/00365549309169664]

139 **Vermeiren AP**, Hoebe CJ, Dukers-Muijrers NH. High non-responsiveness of males and the elderly to standard hepatitis B vaccination among a large cohort of healthy employees. *J Clin Virol* 2013; **58**: 262-264 [PMID: 23895931 DOI: 10.1016/j.jcv.2013.07.003]

140 **Halliday ML**, Rankin JG, Bristow NJ, Coates RA, Corey PN, Strickler AC. A randomized double-blind clinical trial of a mammalian cell-derived recombinant DNA hepatitis B vaccine compared with a plasma-derived vaccine. *Arch Intern Med* 1990; **150**: 1195-1200 [PMID: 2141247 DOI: 10.1001/archinte.150.6.1195]

141 **Nagafuchi S**, Kashiwagi S, Okada K, Anzai K, Nakamura M, Nishimura Y, Sasazuki T, Niho Y. Reversal of nonresponders and postexposure prophylaxis by intradermal hepatitis B vaccination in Japanese medical personnel. *JAMA* 1991; **265**: 2679-2683 [PMID: 1827167]

142 **Playford EG**, Hogan PG, Bansal AS, Harrison K, Drummond D, Looke DF, Whitby M. Intradermal recombinant hepatitis B vaccine for healthcare workers who fail to respond to intramuscular vaccine. *Infect Control Hosp Epidemiol* 2002; **23**: 87-90 [PMID: 11894838 DOI: 10.1086/502012]

143 **Ghebrehewet S**, Baxter D, Falconer M, Paver K. Intradermal recombinant hepatitis B vaccination (IDRV) for non-responsive healthcare workers (HCWs). *Hum Vaccin* 2008; **4**: 280-285 [PMID: 18398298 DOI: 10.4161/hv.4.4.5687]

144 **Chen W**, Gluud C. Vaccines for preventing hepatitis B in health-care workers. *Cochrane Database Syst Rev* 2005; : CD000100 [PMID: 16235273]

145 **Arevalo JA**, Washington AE. Cost-effectiveness of prenatal screening and immunization for hepatitis B virus. *JAMA* 1988; **259**: 365-369 [PMID: 2961895 DOI: 10.1001/jama.1988.03720030025027]

146 **Ginsberg GM**, Shouval D. Cost-benefit analysis of a nationwide neonatal inoculation programme against hepatitis B in an area of intermediate endemicity. *J Epidemiol Community Health* 1992; **46**: 587-594 [PMID: 1494073 DOI: 10.1136/jech.46.6.587]

147 **Avazova D**, Kurbanov F, Tanaka Y, Sugiyama M, Radchenko I, Ruziev D, Musabaev E, Mizokami M. Hepatitis B virus transmission pattern and vaccination efficiency in Uzbekistan. *J Med Virol* 2008; **80**: 217-224 [PMID: 18098129 DOI: 10.1002/jmv.21035]

148 Are booster immunisations needed for lifelong hepatitis B immunity? European Consensus Group on Hepatitis B Immunity. *Lancet* 2000; **355**: 561-565 [PMID: 10683019 DOI: 10.1016/S0140-6736(99)07239-6]

149 **Leonardi S**, Leggio T, Barone P, Sciacca A, Musumeci S. Immune response of subjects at high risk of hepatitis B to a new genetically engineered hepatitis B vaccine administered in low doses by the intradermal route. *Acta Paediatr Jpn* 1990; **32**: 361-364 [PMID: 2288216]

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**Table 1 Studies published since 1983 on vaccination against hepatitis B virus by intradermal route and percentage of positive response**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Categories of patients** | **Patients (*n*)** | **Dose for ID administration** | **Positive response** |
| Marangi *et al*[75] | Chronic kidney disease | 5 | 5 ìg/dose until the protective titer | 100% |
| Fabrizi *et al*[76] | Chronic kidney disease | 25 | 16 doses of 5 ìg/dose | 100% |
| Chanchairujira *et al*[77] | Chronic kidney disease | 25 | 7 doses of 10 ìg/dose every 2 wk | 92% at 7 mo |
| Barraclough *et al[*78] | Chronic kidney disease | 30 | 10 ìg/dose every week for 8 wk | 79% at 24 mo |
| Bunupuradah *et al[*113] | HIV- children | 41 | 2 ìg/dose at mo 0, 2 and 6 | 90.2% at month 7 |
| Launay *et al*[112] | HIV- adults | 144 | 4 ìg × four doses at weeks 0, 4, 8, and 24 | 77% at week 28 |
| Dhillon *et al*[114] | Chronic liver disease | 42 | 40 ìg/dose maximum of three doses | 69% after the thirddose |
| Leonardi *et al*[126] | Celiac disease | 20 | 2 ìg/dose maximum of four doses | 90% |
| Leonardi *et al*[127] | Celiac disease | 30 | 2 ìg/dose x four o five doses every 4 wk | 90% after the third dose |
| Li Volti *et al[*134] | Insulin-dependent diabetes mellitus | 9 | 3 ìg/dose at the start of the study and at two, four, and six or eight week intervals | 77.7% |
| Leonardi *et al[*45] | Thalassaemia | 54 | 5 ìg/dose every two weeks until the protective titer | 96.4% |
| Ghebrehewet *et al*[146] | Healthcare workers | 23 | Two doses of 20 ìg | 91.3% after 1 or 2 doses |
| Hayashi *et al[*138] | Mentally retardation | 63 | 4 ìg/dose maximum of three doses | 93.5% |
| Heijtink *et al*[139] | Mentally retarded patients | 92 | 2 ìg/dose maximum of four doses | 92% |
| Hayashi *et al[*140] | Mentally retarded patients | 62 | 4 ìg/dose maximum of three doses | 93.5% |

ID: Intradermal; HIV: Human immunodeficiency virus.