EDITORIAL

Hepatitis B Vaccination Strategy in HIV-infected Children

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Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) share common risk factors and modes of transmission [1]. Co-infection with HBV and HIV can increase the risk of dying by upto 8 times [2]. HIV-infected children are also particularly vulnerable to reactivation of occult hepatitis-B infection, progression of HBV infection to chronicity, and lower rates of loss of serum HBe antigen following infection [3]. It is therefore important to prevent hepatitis B virus infection in HIV-infected children.

Following Hepatitis B vaccination, antibody to hepatitis-B surface antigen (anti-HBs) levels ≥10 mIU/mL (measured by ELISA) is indicative of protective response. However, vaccine response to standard hepatitis-B vaccination is often blunted in HIV-infected children due to depletion of CD4+ T-cells, and altered distribution of T-cell and B-cell subsets. A decline in the total memory B cells (CD27+) and expansion of immature B cells (CD10+) makes this population susceptible to a high rate of reinfection and waning vaccination-induced immunity [4]. The response rates to the 'classic' hepatitis-B vaccination schedule (10 µg at months 0-1-6) are much lower in children living with HIV compared to HIV non-infected children [5-9].

To achieve higher seroprotection rates, various vaccination strategies have been tried in these children, including the use of double-dose hepatitis-B vaccine [10,11], additional doses of vaccination [10], intradermal route of vaccination [12], varying vaccination schedules (0-1-6 months, 0-1-2 months, 0-1-12 months, *etc*.), and the use of combination vaccines [11]. A meta-analysis by Ni, *et al*. [13] recommends the use of increased dose of hepatitis-B vaccine for achieving adequate seroconversion after primary immunization in HIV-infected individuals.

These studies of hepatitis B vaccination in HIV-infected children are difficult to compare because of varied study designs and heterogeneous populations, disease and treatment status of subjects (***Table* I**) [5-12,14]. There is no consensus, yet, regarding the best hepatitis-B vaccine schedule for primary immunization in HIV-infected children. ***Table* II** summarizes the recommendations on hepatitis B vaccination in HIV-infected children as advocated by various scientific bodies [15-18].

Factors shown to be associated with improved response to hepatitis-B vaccination include higher CD4 counts, undetectable HIV-1 viral load, younger age, increased dose and number of vaccines, and receipt of anti-retroviral therapy (ART) [19]. The use of ART is instrumental in viral suppression and restoration of immune functions, especially if initiated early in life. In several developing countries, HIV-infected children may not have access to ART until the CD4+ counts fall below the cut-offs of severe immunodeficiency, or until they get categorized as Stage 3 or 4 based on WHO Clinical staging of HIV-infection. The study by Siddiqui, *et al.* [14], published in the current issue of *Indian Pediatrics*, seems particularly relevant in a time of introduction of universal ART for HIV-infected children in India by National AIDS Control Organization (NACO) irrespective of their clinical or immunological staging. In this study, only a quarter of children (13/55) were receiving ART, which could explain the low rate of seroprotection. The study by Bunupurudah, *et al.* [12] was able to achieve 92.3% seroprotection in children (about 90% of who were receiving ART) with recombinant hepatitis-B vaccine in a standard dose (10 µg) administered in a three-dose schedule. About 50% of these Thai children were able to mount a good seroprotection response (anti-HBs titers >100 mIU/mL). Siddiqui and colleagues [14] did not compare the proportion of good responders and the long-term immunity against hepatitis-B between the two groups. The study also has a major drawback in terms of a small sample size. No recommendation is possible based on the results of this study, though, it does add to the available scant data.

TABLE I IMMUNOGENICITY OF HEPATITIS B VACCINE IN HIV-INFECTED CHILDREN

Study Group (Year)	*Dose and route*	*Number of doses (schedule)*	*Proportion on ART*	*Seroconversion*
Siddiqui, *et al.* (2017) [14]	10 µg IM *vs* 20 µg IM	3 (0-1-6 mo)	25% in 10 µg IM group *vs* 22.2% in 20 µg IM group	60.8% in 10 µg IM group *vs* 74% in 20 µg IM group
Bose, *et al.* (2016) [10]	20 µg IM	4 (0-1-2-6 mo)	81.8%	94%
Bunupurudah, *et al.* (2011) [12]	10 µg IM *vs* 2 µg ID	3 (0-2-6 mo)	91.3% on ART IM: 87.2% ID:95.1%	90.2% in ID *vs.* 92.3% in IM; 56.1% had good response (Anti HBs >100 mIU/mL) to Hepatitis B vaccination in ID group compared to 82.1% in IM group (*P*=0.01)
Flynn, *et al.* (2011) [11]	20 µg IM *vs* 40 µg IM *vs*Twinrix (20 µg HBs antigen & 720 ELU HAV antigen)	3 (0-1-6 mo)	20 µg IM: 42% 40 µg IM: 40% Twinrix: 49%	60% in the 20 µg IM group *vs* 73.2% in 40 73.2% *vs* 75.45% in Twinrix group
Pippi, *et al.* (2008) [9]	5 µg IM	3 (0-1-6 mo)	52.8%	59.5% (70.8% in ART *vs* 44.4% in non-ART)
Thaithumyanon, *et al.* (2002) [6]	10 µg IM	3 (0-1-6 mo)	-	71.4%
Rutstein, *et al.* (1994) [7]	10 µg IM	3 (0-1-6 mo)	-	35%
Diamant, *et al.* (1993) [8]	10 µg IM	3 (0-1-6 mo)	8%	25%
Zuin, *et al.* (1992) [5]	10 µg IM	3 (0-1-6 mo)	-	78%

ART: anti-retroviral therapy, ELU: ELISA units, HAV: Hepatitis A virus, ID: intradermal route, IM: intramuscular route.

TABLE II RECOMMENDATIONS OF HEPATITIS B VACCINATION IN HIV-INFECTED CHILDREN

Scientific Body	*Dose of Hepatitis B vaccine*	*Schedule*
Centers For Disease Control and Prevention (CDC) [15]	Double dose 20 µg	Three doses (0, 1-2, 4-6 months), IM
National Institute of Health (NIH) [16]	Standard dose 10 µg	Three doses (0, 1-2 months, 6-18 months), IM
Children's HIV Association (CHIVA) [17]	Double dose 20 µg	Three doses (0, 1-2 and 12 months), IM
Indian Academy of Pediatrics (IAP) [18]	Double dose 20 µg	Symptomatic HIV: Four doses (0,1,2,6 months), IM Asymptomatic HIV: Three doses (0-1-6 months), IM

IM: intramuscular route.

There is a need for studies evaluating immune response to hepatitis B vaccine in HIV-infected children receiving ART (as per current guidelines) to establish optimal vaccination schedule. It may be relevant to explore if the schedule needs to be tailored to suit different categories based on immune status measured by CD4 counts.

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