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Immune reconstitution and vaccination outcome in HIV-1 infected children

Present knowledge and future directions

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Current evidence on routine immunization of HIV-1 infected children point out the need for a special vaccine schedule in this population. However, optimal strategies for identifying individuals susceptible to infections, and then offering them sustained protection through appropriate immunization schedule, both in terms of timing and number of vaccine doses, still remain to be elucidated.

Understanding the degree of immune recovery after HAART initiation is important in guiding administration of routine vaccination in HIV-1 infected children. Although quantitative measures (e.g., CD4+ T-cell counts and immunoglobulin levels) are frequently performed to evaluate immune parameters, these measures do not fully mirror functional immune recovery. Here, we will review the status of single mandatory and recommended vaccines for HIV-1 infected children in relation to immune recovery after HAART initiation with the aim of identifying new means to help design personalized vaccine schedules for this population.

Introduction

The establishment of long-term serologic memory relies on the generation and maintenance of antigen-specific memory CD4+ T-cells and memory B-cells.[1] These are generally resting cells capable of re-circulating between the periphery and the lymphoid tissues.[2,3] Upon re-infection, and in the presence of cognate help from CD4+ T-cells, memory B-cells organize germinal center reactions in lymphoid tissues and promptly differentiate to plasma cells with production of high-affinity antibodies in the periphery.[2,3]

Infection with HIV-1 results in a dramatic depletion of CD4+ T-cells and an altered distribution of T-cell subsets. HIV-1 specific central memory CD4+ T-cells (CD45RA-CCR7+) are preferentially depleted while naıve T-cells, both CD4+ and CD8+, are stimulated to enter the circulation and to differentiate into effector memory (CD45RA+CCR7-) and activated memory (CD45RA-CCR7-) cells.[4-6] Persistent viremia has been shown to induce increased expression of activation markers such as HLADR and CD38 on these T-cell subsets.[7,8] In parallel, a higher expression of the pro-apoptotic receptor FAS (CD95) on CD4+ T-cells[9-11] and a positive correlation between the expression of these markers on T-cells and the disease progression of both HIV-infected adults and children has also been reported.[12,13]

The distribution of B-cell subsets is also altered in HIV-1 infected patients with a major decline of total memory (CD27+) and an expansion of immature-transitional (CD10+) B-cells.[14-16] In some cases, the loss of total memory B-cells directly determines the loss of serologic memory gained during natural infections or through routine childhood vaccinations, rendering these patients even succeptible to previously-encountered infections.[17,18] HIV-1 is unable to directly infect B-cells because of the lack of CD4 expression on the B-cell surface. However, interaction of HIV-1 envelope glycoproteins with B-cells has been reported to alter their ability to proliferate and to undergo antibody affinity maturation.[19-22] Polyclonal B-cell activation, hypergammaglobulinemia in parallel with high spontaneous autoantibody production in vitro and an increased incidence of B-cell malignancies have all been reported.[23-26] In general, B-cells are hyper-activated during HIV-1 infection and easily acquire an exhausted phenotype increasing their rate of spontaneous apoptosis.[27-29] Polyclonal B-cell activation and hypergammaglobulinemia increase with viremia while their levels inversely correlate to the CD4+ T-cell percentage.[30] Altogether, both HIV-1 virus per se and the lack of T-/B-cell interactions in the germinal center may be detrimental for memory B-cells and account for their exhaustion and depletion through apoptosis.[31,32]

The above described dysfunctions of the T- and B-cell compartment occur during the early course of HIV-1 infection and have similar dynamics in both adults and children.[33] Successful viral suppression through HAART is able to restore CD4+ T-cells and to normalize the percentage of B-cell subsets in blood only when therapy is applied during primary infection.[34,35] In this respect, we and others have suggested that HAART should be applied early after birth in HIV-1 vertically infected children. An early initiation of HAART is associated with a normal development of the T-cell repertoire, and with preservation of high

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numbers of functional memory B-cells in this population including HIV-1 specific responses.[36-39] However, currently HIV-1 infected children in developing countries do often have access to HAART late in childhood and receive some of the routine immunizations, i. e. against tuberculosis, poliomyelitis, diphtheria, tetanus and pertussis, within the first weeks of life before being treated, most likely, when ongoing HIV-1 replication reaches its highest level.[40,41]

Vaccination in HIV-1 Infected Children and General Current Recommendations

Routine childhood vaccination is among the most effective clinical interventions to prevent disease as it is estimated to save over 3 million lives a year.[42] However, most vaccines that are currently used in the clinic have been developed through relatively simple and largely empirical approaches where efficacy has been tested mostly in healthy populations. Variation in the ability to mount protective immune responses remains problematic for designing and deploying vaccines to subjects with a compromised immune system. Even for the healthy pediatric population, immunization schedules are being continuously up-dated according to new scientific knowledge, epidemiology and new types of vaccines.[43] Moreover, the standard vaccination calendar for mandatory and recommended immunization in healthy children varies among different countries.[43] For HIV-1 infected individuals, many uncertainties remain about optimal strategies for identifying susceptible individuals to infections, and for offering them sustained protection through the correct immunization schedule in terms of pre-defined timing and number of vaccine doses rather than undergoing re-vaccination upon failure of immunization.[44] Recently, the Pediatric European Network for Treatment of AIDS (PENTA) provided recommendations, based on analyses from the literature, on how existing immunization should be best modified for HIV-1 positive children living in Europe. According to this analysis, earlier immunization and compressed booster doses are suggested for most childhood vaccines.[43] However, predictive markers for the ability to develop and maintain protective immune responses to vaccinations and measures for correlates of protection in this population still remain elusive.

Although quantitative measures (e.g., assays of $CD4^+$ T-lymphocyte number and immunoglobulin levels) are frequently performed to evaluate immune recovery, these measures do not fully assess functional recovery. Understanding the degree of functional immune recovery after HAART initiation may be important in guiding vaccine administration.[45]

Adaptive Immune Response to Different Vaccine Types

Childhood vaccines can be divided into 2 main categories: non-replicating and replicating vaccines. Non-replicating vaccines can be further sub-divided into killed/inactivated, subunit and conjugated vaccines while replicating vaccines are exclusively live-attenuated (**Table 1**).

Killed/inactivated vaccines consist of viruses or bacteria that are grown in culture and then killed or inactivated by heat or formaldehyde. Although killed/inactivated pathogens are unable to replicate, the virus capsid proteins or bacterial wall remain intact and can therefore be recognized by the immune system. Subunit vaccines are instead based on a specific protein isolated from a virus or bacterium. Immunization to several encapsulated bacteria is primarily achieved by the administration of non-replicating vaccines based on capsular polysaccharides. However, these latter vaccines are poorly immunogenic and often elicit a B-cell response in the absence of a good memory T-cell response.[46] Thus, in order to provide increased T-cell help from $CD4^+$ T helper 2 cells (Th2) and improved immune responses some bacterial vaccines have been conjugated to different types of immunogens. Nonetheless, in order to maintain protective levels of antibodies over-time after vaccination, non-replicating vaccines require booster doses.

Live attenuated vaccines consist of live viruses or bacteria which have been subjected to repeated passaging into different host cell cultures or culturing at suboptimal conditions thus allowing selection of less virulent strains. Live attenuated pathogens usually undergo slow replication restricted to the site of injection; therefore with such vaccines, boosters may not be required. Unlikely to non-replicating vaccines, live attenuated vaccines elicit a strong T-cell response, from both Th2, Th1 and Cytotoxic T-cells (Tc) for virus vaccines. Therefore, as a consequence of $CD4^+$ T-cell depletion, HIV-1 infected individuals respond poorly to immunization and both adults and children experience rapid waning of immunity.[47-50] In addition, live attenuated vaccines are considered particularly risky for HIV-1 infected children with a compromised immune system as failure of immunization or reversion to virulence may cause disease.

Below, we will review the status of single mandatory and recommended vaccines for HIV-1 infected children in relation to immune recovery (mainly in terms of HIV-1 viral suppression, $CD4^+$ T-cell recovery and B-cell status) after HAART initiation compared with the vaccination outcome of healthy controls with the aim of identifying new means to help design personalized vaccine schedules for these children.

Diphtheria, tetanus and pertussis (DTP). Vaccines against diphtheria, tetanus and pertussis (DTP) include several variants of which the most common is called DTaP. This vaccine contains diphtheria and tetanus toxoids together with acellular components (3 or 5 component variants) of the organism that causes pertussis. However, pertussis vaccines can either be whole cell. DTaP is administered to children while a different formulation called Tdap (with reduced concentration of DT and pertussis proteins) to young adults. Another variant of these vaccines containing the whole-cell, inactivated pertussis pathogen (aka DTP or DTwP) exists and although more effective in conferring immunity, it is not preferred to DTaP for administration in children as it considered more reactogenic and possibly less safe.[51] For tetanus and diphtheria toxoids, positive responses are indicated by ELISA with a minimal cut-off of 0.01 IU/mL with optimal levels of 0.1 IU/mL or by LPA with SI above 3.[52,53]

Table 1. Adaptive immune response to different vaccine types

Vaccine	Vaccine type	Type of immune response	Suggested serological cut-off for protective immunity in the healthy population[43]	Alternative correlates of protection studied in HIV-1 infected individuals	Possible predictive markers of responsiveness for HIV-1 infected individuals
Diphtheria toxin	Killed/inactivated	Th2, B-cells	0.01–0.1 IU/mL	LPA: SI > 3[52,53]	?
Tetanus toxin	Killed/inactivated	Th2, B-cells	0.01–0.1 IU/mL	LPA: SI > 3[52,53]	Older age?[60] Early HAART?[36]
Hepatitis B	Subunit or recombinant	Th2, B-cells	10mIU/mL	?	$CD4^+$ T-cell percentages?[71-73] Short intervals between vaccinations?[71-73]
Influenza	Killed/inactivated	Th2, B-cells	HAI: titer ≥ 40 or ≥ 4-fold antibody increase from baseline	Antigen-specific B-cell ELISpot1[22]	IL-21R upregulation on B cells and high levels of blood IL-21?[90]
Pneumococcus (serotype specific)	Conjugated	Th2, B-cells	0.35 μg/mL	> 2-fold antibody increase from baseline[93] OPA: titer ≥ 8[92] Antigen-specific B-cell ELISpot[98]	Early HAART?[36]
Meningococcus	Conjugated	Th2, B-cells	SBA: titer ≥ 4 or ≥ 8	?	?
HiB	Conjugated	Th2, B-cells	0.15–1 μg/mL	75 ng/mL[61]	?
Measles	Live attenuated	Th2, B-cells, Th1, Tc	0.12–0.32 IU/mL	EIA: 9.0 AU/mL[53,104,105] Antigen-specific B-cell ELISpot[36]	HIV-1 viral load before HAART and $CD4^+$ T-cell counts after HAART?[60] Early HAART?[36]
Mumps	Live attenuated	Th2, B-cells, Th1, Tc	2 ELU/mL	EIA: 9.0 AU/mL[53,104,105]	?
Rubella	Live attenuated	Th2, B-cells, Th1, Tc	> 10–15 IU/mL	EIA: 10.0 AU/mL[53,104,105]	?
Varicella	Live attenuated	Th2, B-cells, Th1, Tc	gpELISA: ≥ 5 IU/mL	FAMA: titer ≥ 1:2[79] LPA: SI > 3[79]	HIV-1 viral load?[79]
Tuberculosis (BCG)	Live attenuated	Th2, B-cells, Th1, Tc	IFN-γ: ? levels	?	?

Standard, alternative and possible predictive markers for evaluating clinical protection upon immunization of HIV-1 infected children. Th1–2, $CD4^+$ T helper 1 or 2 cells; Tc, $CD8^+$ Cytotoxic T-cells; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immunosorbent spot; FAMA, fluorescent antibody membrane assay; gpELISA, glycoprotein ELISA; HAI, haemagglutination inhibition assay, LPA, lymphoproliferation assay; OPA, opsonophagocytic activity assay; SBA, serum bactericidal antibody assay; SI, stimulation index.

Many studies on DTP (mostly analyzing immunity to tetanus toxoid) involving re-vaccination of children on HAART are available.[52,54-61] The percentage of initial responders to vaccination ranged 53–100% among different studies[52,56,58-61] while in general, a high percentage of children (up to 90%) maintained immunity to tetanus for 1 y after vaccination.[52,59,61] Only one study reported a significant decline in the percentage of responders (from 74% to 38%) before 1 y from vaccination.[56] For pertussis, the antibody concentration was analyzed in one study showing a decline over-time (from 22.3 EU/mL at 2 mo to 6.8 EU/mL at 2 y from vaccination).[57] Lymphoproliferative responses within 3 mo from vaccination were also evaluated for tetanus toxoid in several studies showing a proportion of 47–86% of responders[52,54,55,59] while one study reported that only 17% of children responded to diphtheria toxoid.[55] The lymphoproliferative response to tetanus toxoid was reported to decrease over-time (from 73% at 1 mo to 61% at 1 y from vaccination).[59]

Both lymphoproliferative responses and antibody levels to tetanus toxoid and pertussis are generally higher for viral controllers presenting with high $CD4^+$ T-cell counts (with or without HAART) and are independent of age.[52,54-57,62-65] Viral suppression after HAART was not associated to immunity to tetanus toxoid in another study.[53] Duration of HAART has also been shown not to play a major role in relation to vaccine responses to tetanus toxoid.[59] However, we have shown that antibodies to tetanus toxoid remain high (to levels comparable to age-matched healthy individuals) for several years after DTP in children treated with HAART before 1 y of age compared with children also having

undetectable HIV-1 viral load and high CD4+ T-cell counts but treated later in time.[36] Altogether, this suggests that early HIV-1 suppression may help preserving the ability of T- and B-cells to respond to DTP in HIV-1 infected children.

Poliomyelitis. The most common vaccine against poliomyelitis is an enhanced potency inactivated poliovirus vaccine (IPV) modified from the Salk original vaccine, which is based on three different types of inactivated poliovirus strains (Mahoney, MEF-1 and Saukett). An alternative to IPV is the oral polio vaccine (OPV), or the Sabin vaccine, which is a live attenuated vaccine mostly preferred in developing countries due to its easy way of administration. Trivalent OPV (TOPV) has been shown to provide longer lasting immunity than the Salk vaccine.[66] However in developed countries, the first scheduled immunization is generally provided to children by either a pentavalent or hexavalent formulation containing IPV, DTaP, and hepatitis B vaccine together with Hemophilus influenzae type B vaccine. The level of serum neutralizing antibodies is usually assessed to determine positive immunization responses to poliovirus vaccines. However, while an antibody cut-off level for protection has not been determined, microneutralization at 1:4–1:8 dilution is thought to indicate protection.[42,67]

Studies on OPV vaccination have mostly been conducted in HIV-1 infected children living in endemic areas, showing post-vaccination immunity to poliovirus in 97% of the children.[67] This high rate of success compared with other live-attenuated vaccines is probably due to the fact that OPV induces excellent immunity in the intestine which is the main site of poliovirus entry.[68]

Hepatitis B. The vaccine against hepatitis B virus (HBV) is a subunit vaccine containing one of the viral envelope proteins, hepatitis B surface antigen (HBsAg). Once HBsAg antibodies and specific immunologic memory arise, infection by hepatitis B can no longer occur in vaccinated individuals.[69] A cut-off of 10 mIU/mL measured by ELISA is indicative of a protective antibody response.[53]

Untreated HIV-1 infected children produce lower antibody levels upon HBV vaccination compared with HAART-treated children and age-matched healthy controls.[70,71] Interesting data on the response to HBV vaccines in HIV-1 infected children can be found in relation to re-vaccination and HAART. Upon re-vaccination, short-term responses to HBV vaccines are consistently variable ranging from 46% to 92% of responders decreasing to 38% after 2 y and to 25% after 4 y from vaccination.[72,73] Among children revaccinated a second time only 37% seroconverted.[73]

Duration of HAART and HIV-1 viral load do not directly correlate with antibody levels.[71-73] However, good CD4+ T-cell percentages (> 25%) both before (nadir) and after application of HAART together with shorter intervals between vaccination and re-vaccination were associated with a better immune response.[71-73] Therefore, a different HBV vaccination outcome among HIV-1 infected children treated with HAART may most likely be due to a different recovery of CD4+ T-cells.

Influenza. Influenza viruses are highly variable; therefore new vaccines need to be developed every year. A trivalent influenza vaccine (TIV) is usually formulated as an injection and contains three killed influenza viruses while a live attenuated influenza vaccine (LAIV) comes as a nasal spray.[74] However, administration of LAIV is not recommended for children under 2 y of age.[75] The strains are chosen according to predictions by the WHO based on strains that will most likely circulate during the next season. A quadrivalent vaccine (nasal spray) was also recently approved and it is expected to be administered during 2012.[76] While the effectiveness and need of influenza vaccination in healthy individuals, both adults and children is still debated,[77] current recommendations for HIV-1 infected patients suggest routine vaccination as these patients may be at risk of complications due to influenza infection.[43] Positive responses to each vaccination are evaluated by haemagglutination inhibition assay (HAI) with titer ≥ 40 or, in order to exclude pre-existing influenza cross reactive antibodies arising in response to different stains, ≥ 4-fold antibody increase from baseline.[78,79] However, some studies suggested that an HAI titer ≥ 40 may not be fully protective in immunocompromized individuals.[80]

In general, protective responses to different inactivated seasonal influenza vaccines in HIV-1 infected children, even if treated with HAART, are lower compared with healthy controls.[79,81-83] The percentage of initial responders ranges 50–100% and in some cases, antibodies are almost completely lost after 6 mo from vaccination.[83] However, the establishment of CD8+ interferon-γ-secreting T-cells together with CD4+ interleukin (IL)-2-secreting T-cells upon vaccination may be more important than antibody formation as increase for influenza specific IgG3 but not IgG1 was reported.[83] On the other hand, higher pre-existing antibodies against influenza were associated with a better response to re-vaccination.[79] The role of HIV-1 viral load for the influenza vaccination outcome is unclear as an association between viral load and immune response was reported in one study but not in another.[60,82] On the other hand, age and CD4+ T-cell counts do not seem to play a role.[79,83]

During 2009, an upcoming pandemic infection of humans with swine influenza virus A(H1N1) was announced by WHO and a massive vaccination campaign was undertaken with both killed virus vaccines and live attenuated nasal sprays. In view of their possible increased susceptibility to morbidity associated with influenza infection as suggested by the Centers for Disease Control and Prevention (CDC),[84,85] most countries gave high priority to the vaccination of HIV-1 infected subjects. Moreover, in order to maximize the likelihood of mounting immune-protection to the A(H1N1) influenza virus, the A(H1N1) influenza immunization schedule often recommended one dose of vaccine for healthy individuals and included additional doses for individuals with a compromised immune system due to age or primary and secondary immune deficiencies thus including HIV-1 infected patients.[84,85] However, the rate of consequences due to natural A(H1N1) infection was similar between HIV-1 infected subjects and healthy controls and the efficacy of diverse formulations of influenza vaccines (with or without different adjuvants coupled to the influenza antigens) in both adults and children, was reported in several studies.[86-89] Nonetheless, the numerous studies undergone during the A(H1N1) pandemic represented a great occasion for increasing the knowledge on immunological

markers possibly predictive of vaccination response. For example, one of these studies proposed upregulation of the interleukin (IL)-21 receptor on B-cells and of IL-21 in plasma as a novel immunological marker to distinguish between 2009 pandemic flu vaccine responders and non-responders.[90] This may suggest that additional immunonological markers, rather than antibody response, may be used for evaluating clinical protection in the HIV-1 infected pediatric population.

Pneumococcus. In adults, a 23-valent pneumococcal non-conjugated polysaccharide vaccine (PPV) against infection by Streptococcus pneumoniae is usually administered once. However, children under the age of two years often fail to mount an adequate response to the 23-valent adult vaccine; therefore several pneumococcal conjugated vaccines (PCV) of which the 7-, 10- and 13-valent formulations have been licensed, are used instead.[91,92]

A serotype-specific cut-off of 0.35 μg/mL measured by ELISA is used to evaluate protective humoral responses to PCV or PPV.[92] However, antibody fold increase (above 2-fold) from baseline rather than arbitrary levels has been suggested to be more accurate as the level of anti-pneumococcus antibodies may increase during opportunistic infections in HIV-1 infected individuals.[93] In addition, the functionality of anti-pneumococcus antibodies may also be evaluated by opsonophagocytic activity assay (OPA). In this respect, a possible better association with protection against some pneumococcal serotypes has been discussed for children vaccinated with diverse formulations of PCV, included in different studies, whose antibodies had a serotype-specific titer of OPA ≥ 8 rather than antibody concentration above the cut-off level of 0.35 μg/mL.[92]

Although many investigations on immunity to Streptococcus pneumoniae in HIV-1 infected patients have been conducted, only a few studies analyzed the role of immune reconstitution upon PCV vaccination (mainly with the 7-valent formulation) in HIV-1 infected children.[94-97] The percentage of initial responders to PCV vaccination ranged from about 30% to over 90% in these studies.[94-97] However, immune responses remained stable over-time (from 2 mo to 2 y after vaccination for all serotypes analyzed).[97] High levels of $CD4^+$ T-cells, lower HIV-1 viral load and longer time on HAART were associated with better responses.[94,97] We previously reported that immunity to pneumococcus was higher in HIV-1 infected children starting HAART during the first year of life, to a level comparable to the one observed for age-matched healthy controls.[36] Nevertheless, in another study HAART treated HIV-1 infected children had lower antibodies to pneumococcus compared with healthy controls.[94] Interestingly in our study, among children treated later in life, similar pneumococcus-specific antibodies were found for HIV-1 viral controllers compared with children undergoing virological failure.[36] Response to the PCV vaccine is mostly mediated by B-cells; in this respect, depletion of B-cell subsets and pneumococcus-specific memory B-cells has recently been reported in HIV-1 infected African children with invasive pneumococcal disease despite a proportion of $CD4^+$ T-cells being over 15%.[98] Therefore, results from these studies suggest that evaluating immune responses to pneumococcal vaccination in HIV-1 infected patients with low $CD4^+$ T-cell counts may be difficult as these patients may be subjected to opportunistic pneumococcal infection due to pathogen reactivation increasing the level of antibodies to pneumococcus independently of vaccination.[99]

Meningococcus (*Neisseria meningitidis*). The meningococcal vaccine is used against infection by *Neisseria meningitidis*. *Neisseria meningitidis* has 13 serogroups of which six (A, B, C, Y, W135 and X) are responsible for disease in humans. Conjugate vaccines against different serogroups are administered according to the most prevalent serogroup in a specific country. For measuring protection, the serum bactericidal antibody (SBA) assay is the method of choice. An SBA titer of ≥ 4 or ≥ 8 is used for indicating protection when using either human or rabbit complement.[100]

Not many studies have evaluated the immunization outcome after meningococcal vaccination in HIV-1 infected children treated with HAART. Only one study on MenC vaccination in Europe reported low immunogenicity in HIV-1 infected children compared with age-matched healthy controls and with no data on waning.[43]

However, recently the IMPAACT P1065 Protocol Team provided data on the safety and immunogenicity of a quadrivalent meningococcal conjugate vaccine (MCV4) in HIV-1 infected children aged between 2 and 10 y, reporting seroprotection for serogroups A and W up to 72 weeks from immunization. A second dose of this vaccine was required to increase the proportion of children responding to serogroup C and Y. However, seroprotection was not maintained for serogroups A and C after 1 y from immunization.[101]

Hemophilus influenzae type b (HiB). The HiB vaccine refers to a conjugate vaccine against the Hemophilus influenzae type b bacterium which is one of the pathogens that can cause early childhood meningitis. Three types of highly effective conjugate vaccines utilizing different proteins in the conjugation process (tetanospasmin, mutant diphtheria protein and meningococcal group B outer membrane protein) exist and the HiB vaccine is usually included in the pentavalent or hexavalent formulation containing IPV, DTaP, and hepatitis B vaccine.[102] Antibody levels above the cut-off of 0.15–1 μg/mL measured by ELISA is considered as indicative of a positive response to vaccination.[42]

A good response to the HiB vaccine has been registered for HIV-1 infected children receiving HAART with about 75% responders with low or absent antibody waning over-time.[61]

Replicating Vaccines (Live Attenuated)

Measles, mumps, rubella (MMR). The MMR vaccine is a mixture of live attenuated measles, mumps and rubella viruses. MMR is generally administered to children between 9 and 16 mo of age. However, even among the healthy population, a small number of individuals (2–5%) fail to develop immunity to measles after the first dose and require re-vaccination.[103] Positive antibody responses and immune protection upon vaccination with MMR have been indicated using different laboratory tests. For measles, a cut-off of 0.12–0.32 international units (IU)/mL measured by Enzyme-linked immunosorbent assay (ELISA) or of 9.0 antibody units (AU)/mL measured by enzyme immune assay

(EIA) are often used while for mumps and rubella a cut-off of 9.0 and 10.0 AU/mL have been respectively used.[53,104,105] Being a live attenuated vaccine, MMR is able to induce both Th2 and Th1/Tc cell-mediated immune responses. However, despite formation of measles specific CD4+ and CD8+ T-cells has been shown to be important for reaching immune-protection upon vaccination,[106] this is not very often evaluated in the clinic. Therefore, there are no available data on cell-mediated immunity to MMR for HIV-1 infected children under HAART.

Several studies measured the development of long-term immunity upon MMR vaccination or re-vaccination in HAART-treated HIV-1 infected children and generally found that immunity decreased with time compared with healthy age-matched controls.[60,61,104,107,108] In particular, in HIV-1 infected children the extent of short-term response (3 mo from vaccination) to MMR was up to about 90% of responders with a subsequent decrease to 40–80% at later time points.[61,105] Therefore, despite HAART-treatment, many HIV-1 infected children do not maintain protective levels of antibodies against measles, mumps and rubella over-time compared with age-matched healthy controls. We found that timing of HAART initiation may play a key role for the establishment of a long-term response to MMR as we reported that children starting HAART before the first year of life developed protective levels of antibodies to measles upon MMR compared with children who started HAART later.[36] Importantly in this study, response to measles in early-treated children was also related with preservation of high numbers of functional memory B-cells suggesting that formation and preservation of antigen-specific memory B-cells may be a predictor of long-term response to vaccination.[36]

HIV-1 viral load, CD4 T-cell counts, immunoglobulin levels and the patient's clinical status are often analyzed before and after HAART in order to evaluate the (predictive) role of the immune system status and of the degree of immune recovery for vaccination response. HIV-1 viral load and CD4+ T-cell counts were predictive of an effective immune response in only one study and only by measuring viremia prior to treatment and CD4+ T-cell levels after the treatment.[60] In several other studies, viral load and CD4+ T-cell levels were not predictive of protective response.[53,60,104] Two studies reported that low levels of antibodies gained during the first MMR vaccination or natural infection, thus before HAART initiation, were predictive of loss of immunity for measles and rubella upon re-vaccination.[60,105] When analyzed, the CDC stage and age at vaccination were not predictive for immunity to measles.[60,104] However in one study, young age was found to be associated with loss of measles antibodies.[105]

Varicella. The vaccine against varicella (commonly known as chickenpox) is a live attenuated Varicella Zoster Virus (VZV). Vaccination against chickenpox is mandatory prior to school entry in North America while it is only recommended in Europe and Australia; therefore not many studies on immune reconstitution and varicella vaccination outcome in HIV-1 infected children have been conducted. The proposed correlates for protection against varicella are a titer ≥ 5 IU/mL measured by glycoprotein (gp) ELISA, a serum neutralization dilution ≥ 1:64 and by fluorescent antibody membrane assay (FAMA) with titer ≥ 1:2.[42,79] VZV belongs to the family of herpes viruses, therefore formation of varicella specific CD8+ T-cells is particularly important to prevent reactivation and infection following vaccination. In view of this, positive responses to vaccination in HIV-1 infected children have also been evaluated by varicella-specific lymphoproliferative assay (LPA) with stimulation indices (SI) above 3.[79,109]

One study analyzed both the short- and the long-term response to the varicella vaccine in HIV-1 infected children reporting that from about 70% of initial antibody responders, the proportion of children with an immune response dropped to 65% after 1 y, to 47% after 2 y and to 38% after 3 y from vaccination.[79] A similar decline on the proportion of children with a positive lymphoproliferative response was reported.[79] Among all HIV-1 infected children, the highest proportion of children developing protective immunity were HAART-treated.[79] In addition, an indirect association between the presence of protective antibody titers and immediate pre-vaccination HIV-1 RNA was reported.[79]

Tuberculosis. Bacillus Calmette-Guérin (BCG) is a live attenuated Mycobacterium bovis for vaccination against Mycobacterium tuberculosis in humans. The BCG vaccine is partially effective (60–80%) in preventing tuberculosis (TB) in healthy individuals and interestingly, its protective effect varies according to geography.[110] Another interesting point in the field of vaccination against TB is that despite not being a virus vaccine, neonatal immune responses to BCG are characterized by formation of both Th2 and Th1 cells of which the latter have been shown to be particularly important for protection against mycobacterial infection.[111,112] The recent description of disseminated cases of mycobaterial infections in patients affected by interferon-gamma (IFN-γ) deficiency, definitively proved the essential role of IFN-γ releasing T-cells in the protection against mycobacteria.[113] The WHO recommends BCG vaccination for all children born in countries highly endemic for TB as it may prevent hematogenous TB including TB meningitis. However administration of BCG is not recommended for HIV-1 infected children as the risk of severe infection may overcome the risk of contracting TB even in endemic areas.[114]

Nonetheless, data on BCG vaccination of HIV-1 infected children are available from a few studies. A retrospective case-control study conducted in Zambia reported no protective effect of BCG vaccination in HIV-1 infected children while a protective effect was observed in about 60% of the healthy children recruited in this study.[115]

The design of clinical trials for evaluating the safety and the efficacy of BCG vaccination in both HIV-1 exposed and HIV-1 infected neonates and children is complicated by several factors including the lack of clinical/immune correlates of protection, the lack of a confirmation of efficacy against disseminated forms of TB in healthy children, by difficulties in diagnosing TB disease in children and finally by the fact that in developing countries, often the HIV-1 status is not known when the BCG vaccine is administered to children (which is soon after birth). Moreover, the role of an early initiation of HAART in children vaccinated with BCG or the potential positive effect of delayed vaccination (after HAART) or re-vaccination is not known. In this respect, it has recently been reported that an early initiation of HAART

reduced the risk of BCG immune reconstitution adenitis in infected children.[116]

Generally, concerns exist on whether in developing countries BCG should be administered at birth to all neonates including children born to HIV-1 infected mothers or whether for such cases, vaccination should be delayed till the HIV-1 seropositivity is evaluated by virological testing. One study recently suggested that delaying BCG vaccination from birth to 10 weeks of age may result in an enhanced memory CD4+ T-cell response in healthy children.[117] This may also be applicable to HIV-1 exposed uninfected infants. However in this respect, further laboratory and clinical studies are needed.

Future Perspectives

In the near future, many efforts are probably going to be made by clinical investigators on the search for novel predictive biomarkers of vaccination response in HIV-1 infected individuals following routine vaccination (**Table 1**). Results on attempts to relate immune reconstitution (HIV-1 viral load and CD4+ T-cell restoration in primis), duration of HAART and age have so far not been coherent between different studies and for different vaccines, and globally remain poorly convincing.

As we discussed in the introduction of this review, many defects have been described for both T- and B-cells during HIV-1 infection as a direct effect of the virus or due to indirect effects. In particular, as an indirect effect, the degree of immune activation has been shown to alter the concentration of cytokines and chemokines in blood having diverse effects on the immune system. It is known for example that the abnormal expansion of immature-transitional B-cells may be related to increased serum levels of IL-7 while increased levels of C-X-C chemokine ligand CXCL13 have been related to the downregulation of C-X-C receptor CXCR5 on the B-cell surface.[16,118] Other interesting factors, yet to be fully explored in the context of response to vaccination, are for instance B-cell Activating Factor (BAFF), A Proliferation Inducing Ligand (APRIL) and IL-21 which concentrations and dynamics have also recently found to be impaired during HIV-1 infection.[90,119]

Another approach for improving humoral responses upon childhood routine vaccination of HIV-1 infected individuals may be the early diagnosis of failure of immunization through the validation of methods for testing vaccine efficacy early after vaccination. For immune responses against some viral pathogens, evaluating the formation and maintenance of antigen-specific memory B-cells rather than antibody concentration may be more reliable.[120] We have for instance identified immune responses to HIV-1 in a group of viral controllers, by detecting HIV-1-specific memory B-cells but not HIV-1-specific antibodies in blood by B-cell Enzyme-linked immunosorbent spot (ELISpot).[36] Similarly, clinical observations up to 10 y after neonatal HBV vaccination indicated that, despite a continued decline of anti-HBV antibody levels to non-protective levels in almost 63% of the vaccines, subclinical infections, did occur only in 1–9% of subjects, and no chronic HBsAg carriers could be reported.[121] These data suggest that vaccine recipients may remain protected against clinical HBV infection through persistent immune memory and anamnestic antibody responses. In this respect, for considering administration of additional boosts the formation of cellular rather than humoral immunity after childhood vaccination may be evaluated by B-cell ELISpot or by alternative approaches. In support of this, the number of publications reporting the set-up of new antigen-specific B-cell ELISpot is increasing in the literature.[36,98,122]

Application of such methods may be beneficial for vaccine design not only for HIV-1 infected patients but also for patients with other primary and secondary immune diseases presenting with similar immune disorders.

Suboptimal antibody production due to defects in B-cell maturation and function is for example the most common feature of human primary immunodeficiency disease. Specific immune responses to polysaccarides have been found to be altered in patients suffering from common variable immune deficiency (CVID).[123] Moreover, patients treated with immunosuppressive therapies after solid organ transplantation or after hematopoietic stem cell transplantation presented reduced and non-protective levels of vaccine-induced antibodies.[124-126] The mechanisms underlying the suboptimal maintenance of protective immune responses are still unclear. Therefore, comparative studies on vaccination of such populations may supplement data on studies of HIV-1 infected patients with the common aim to improve the rate of immunization success.

Conclusions

Despite successful HAART, HIV-1 infected children are characterized by a low responsiveness to routine childhood immunizations with rapid waning of immunity compared with healthy individuals. Timing of HAART initiation is the major factor predicting the longevity of memory responses and immune protection in vaccinated HIV-1 infected subjects.[36,122] Thus, early HAART should be applied to all vertically HIV-1 infected infants prior to undergoing childhood immunization.[127] However, to date the early treated patients represent the minority of the HIV-1 infected pediatric population. Hence, special vaccination is required for the large population of children who started the treatment during the chronic phases of the infection.

Despite new knowledge in the field of cellular immunity has led to new immunological read-outs potentially important as correlates of vaccine induced protection, currently none of such correlates has been sufficiently validated for immune compromised individuals.[128]

As we have discussed throughout this review, immune responses to different types of vaccines are complex and elicit different types of immune responses (**Table 1**). Evaluating immune protection exclusively with antibody cut-off levels might be imperfect, particularly for immune compromised patients. Indeed, vaccine preventable infectious diseases have been reported among these patients despite the presence of "protective" antibody titers.[129] Cellular immunity and the possible predictive role of different cytokines, survival and environmental factors supporting both T- and B-cell responses during vaccination (beyond

Table 2. Key points and future directions to increase vaccines-induced protection in HIV infected children.

Key points
• HAART, started in the late phases of disease is not able to provide a full recovery of protective memory responses.
• HIV-1 infected children present lower responses to vaccination and more rapid waning of immunity compared with healthy individuals.
• Complete immune reconstitution should be achieved before vaccination in order to obtain a protective and long lasting immune response.
• Currently available serological markers of immune response may not be predictive of protection from vaccine-preventable infections in immune compromised patients.
Future directions
• Provide early HAART to HIV-1 infected infants in order to control viremia and fully reconstitute the immune system prior to vaccination.
• Identify additional and more specific correlates of protective vaccination responses in immune compromised patients.
• Design, through the identification of novel biomarkers predictive of protective vaccination, a personalized vaccination schedule among cohorts of immune compromised patients.

antibody levels, $CD4^+$ T-cell counts and HIV-1 viremia) must then be explored with the aim of identifying new additional correlates of immune protection and novel predictive biomarkers of vaccination response (**Table 2**).

Before such new biomarkers are available, personalized vaccination schedules may be designed based on timing of HAART initiation and on current serological biomarkers.[43] In parallel, new methods to early identify the waning of protective immunity following vaccination must be validated for immune compromised patients in order to anticipate re-immunization before the infection occurs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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