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# Immunization in Patients with HIV Infection

## Are Practical Recommendations Possible?

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## Abstract

The purpose of this article is to review immunization recommendations for HIV-infected individuals in resource-constrained countries, particularly in sub-Saharan Africa.

Recent evidence suggests that HIV-infected children are at risk for low immunization coverage in sub-Saharan Africa. Routine immunization is recommended for these children. In comparison with immunocompetent children, recommendations for live-attenuated vaccines differ in HIV-infected children. However, limited laboratory capacity to diagnose HIV infection amongst young children prevents the implementation of these HIV-specific guidelines in resource-constrained countries. Re-immunization has been the focus of recent research in high- and middle-income countries. Findings show that children established on highly active antiretroviral therapy have suboptimal vaccine-specific immunity and may benefit from re-immunization. Before re-immunization guidelines can be formulated for resource-constrained countries, several questions should be addressed, including whether all HIV-infected children will benefit from routine re-immunization and what optimal number of vaccine doses should be administered. Pneumococcal and influenza infections are important causes of morbidity and mortality amongst HIV-infected individuals. There is compelling evidence showing that pneumococcal conjugate vaccines will protect HIV-infected and uninfected children against invasive infection. Pneumococcal conjugate vaccines should be prioritized for introduction in countries with high HIV prevalence. Although, annual influenza immunization is recommended for HIV-infected individuals, the effectiveness in Africa remains unclear.

In conclusion, this brief overview has identified several limitations of current immunization policy and practice for HIV-infected individuals living in resource-constrained countries.

Routine immunization is considered one of the most important public health interventions. The WHO recently documented steady improvement in routine childhood immunization coverage, worldwide. The African region continues to experience relatively lower primary immunization coverage rates. In 2005, coverage was 72% for three doses of diphtheria-tetanus-pertussis vaccine compared with the global average of 86%; 70% for three doses of trivalent oral poliomyelitis vaccine compared with

the global average of 85%; 45% coverage for three doses of hepatitis B vaccine compared with the global average of 57%; and 68% coverage for one dose of live-attenuated measles vaccine compared with the global average of 84%.[1] Since 2000, improved immunization coverage against measles has been associated with significantly reduced mortality in Africa.[2] Disruption of routine poliomyelitis immunization in Northern Nigeria from 2002 onwards led to a resurgence of wild type-1 poliomyelitis and the subsequent exportation of poliomyelitis to 11 African countries. Over the last 2–3 years, intensified immunization campaigns have again reduced the global burden of poliomyelitis. Total global eradication remains an elusive goal and probably will not be attained during the next 10 years.[3]

Routine pneumococcal conjugate and rotavirus immunization has yet to be introduced in most low- and middle-income countries. The addition of the 7-valent pneumococcal conjugate vaccine to national immunization schedules is considered a priority in countries with high HIV prevalence because of high associated pneumococcal disease burden and mortality. Current constraints to implementation include the high cost of both vaccines and the uncertain efficacy for the new generation of rotavirus vaccines in Africa and Asia. Efficacy trials are currently being conducted in these regions.[4,5] Although routine immunization is traditionally considered a childhood intervention, adolescents and adults are increasingly being included in immunization programmes. The licensing of several newer vaccines, including acellular pertussis, human papillomavirus and polyvalent meningococcal conjugate vaccines, has influenced this trend.[6,7]

At present, 33.2 million people are estimated to be living with HIV infection, of whom 2.5 million are children. Approximately two in every three adults and nearly 90% of children with HIV live on the African continent.[8] By December 2006, of an estimated 7.1 million in need, about 2 million (28%) HIV-infected individuals were receiving highly active antiretroviral therapy (HAART). Sub-Saharan Africa had more than 1.3 million adults and children receiving HAART.[9] High annual death rates among HIV-infected people emphasise the unmet need for HAART.

The relationship between HIV infection and immunological response to immunization is complex. HIV infection compromises both T- and B-lymphocyte function, impacting negatively on quantitative and qualitative responses to vaccine antigens.[10,11] Despite the positive effects of immunological reconstitution, HAART only partially improves B-lymphocyte immunity and humoral response to immunization. HAART is associated with increased B-lymphocyte number but defects of memory B lymphocytes persist. HIV infection causes marked reduction in IgM memory $CD19^+$ $CD27^+$ $IgM^{High}$ $IgD^{Low}$ $CD21^{High}$ B-lymphocyte percentage, which is not restored by HAART. In addition, approximately 25% of HIV-infected individuals receiving HAART have markedly reduced switched memory $CD19^+$ $CD27^+$ $IgM^-$ $IgD^-$ B-lymphocyte percentage. These two memory subset defects correlated with impaired responses to pneumococcal polysaccharide and tetanus toxoid vaccines, respectively, in patients receiving HAART.[12]

In this article, recent developments regarding the immunization of HIV-infected individuals are summarized and the resultant practical implications discussed with reference to impoverished settings, particularly in sub-Saharan Africa. Previous reviews have analysed in greater depth the safety, immunogenicity and efficacy of common childhood vaccines in HIV-infected children.[13,14]

## 1. Routine Childhood Immunization

Since the launch of the expanded programme on immunization in 1974, several position papers on vaccine preventable illnesses have influenced immunization practice in low- and middle-income countries.[15] A recent study from Zambia showed that HIV infection was a significant risk factor for low immunization coverage. HIV-infected children were approximately twice as likely to be incompletely immunized compared with uninfected children. Despite the existence of guidelines for immunizing HIV-infected children, high HIV prevalence settings are associated with frequently missed op-

portunities for immunization, increasing the risk for vaccine-preventable illnesses.[16]

Routine immunization recommendations for HIV-infected children are similar to those in uninfected children with notable exceptions relating to live-attenuated vaccines.

### 1.1 Bacille Calmette-Guérin

Recent studies from Argentina and South Africa showed that HIV-infected children immunized with Bacille Calmette-Guérin (BCG) vaccine at birth and who subsequently progress to advanced HIV disease or AIDS are at a significantly higher risk for developing disseminated BCG infection. Therefore, in HIV-infected children, the risks of immunization outweighs potential benefits.[17,18] Consequently, the Global Advisory Committee on Vaccine Safety has recommended that all children who are known to be HIV-infected, even if asymptomatic, should no longer receive the BCG vaccine. Because HIV testing during infancy is not widely available in most resource-limited countries, neonatal BCG continues to be administered to all infants, perpetuating the risk to HIV-infected infants. Where early HIV testing is possible, BCG immunization should be deferred until the HIV status of infants has been established and should only be administered to infants who are not infected with HIV.[19]

### 1.2 Measles

Measles immunization is recommended for all susceptible children, including HIV-infected children with asymptomatic disease. In countries where measles remains endemic, early immunization is recommended in healthy HIV-negative children, usually at 9 months of age. HIV-infected infants should be immunized at 6 months of age and an additional dose issued at 9 months. In addition to the 6- and 9-month doses, a booster at 15–18 months is recommended for all children.[20] A recent study explored the age at which passively acquired maternal neutralizing antibodies to the measles virus are lost. By 6 months of age, 91.1% of HIV-infected children, 83.3% of HIV-exposed but uninfected infants, and 57.7% of HIV-negative infants had non-protective antibody titres, supporting early measles immunization in HIV-infected children from 6 months of age onwards.[21]

### 1.3 Yellow Fever and Poliomyelitis

All individuals aged 9 months or older in yellow fever endemic areas should be immunized with the live-attenuated vaccine. Exceptions include severely immunosuppressed individuals and those with symptomatic HIV infection, where there is concern that immunization may cause disease.[22] There are limited data on the immunogenicity of yellow fever vaccine in HIV-infected individuals. In one small study conducted in Côte d'Ivoire (Ivory Coast), only 17% (3 of 18) of HIV-infected children achieved an adequate antibody response compared with 74% (42 of 57) of HIV-uninfected children after immunization. None of the immunized children developed yellow fever during a median follow-up period of 29 months.[23]

Global poliomyelitis eradication strategy is based on live oral poliomyelitis vaccine. In HIV-infected children, oral poliomyelitis vaccine is immunogenic. In one study, 97% of HIV-infected children achieved protective antibody titres to poliovirus types 1, 2 and 3 after three doses of the vaccine. Geometric mean antibody titres were significantly lower in HIV-infected children compared with uninfected children.[24] The risk for vaccine-associated paralytic poliomyelitis (VAPP) is increased in primary antibody disorders. By contrast, only two HIV-infected children have been reported to develop VAPP.[13] Therefore, recommendations for immunizing HIV-infected children are identical to those for uninfected children.[13]

An impediment limiting the implementation of these live-attenuated vaccine recommendations in resource-constrained countries relates to the diagnosis of HIV infection in young children. In children less than 18 months of age, diagnosis relies on HIV DNA polymerase chain reaction (PCR) or ultrasensitive p24 antigen assays. These tests are relatively expensive and PCR technology is not widely available in routine laboratories in resource-constrained

settings with high HIV prevalence, which creates a significant barrier to implementing global policy.

## 2. Is There a Role for Re-Immunization?

Recent publications have explored the relationship between HAART, immunogenicity during primary childhood immunization, and vaccine-induced responses following the administration of booster doses or re-immunization. In one of the first studies undertaken, of 19 previously immunized children (median age 7 years) with favourable quantitative CD4+ T-cell responses to HAART (median CD4+ cell percentage and CD4+ cell count at the time of re-immunization was 35% and 944 cells/mm$^3$, respectively) and an average duration on HAART of 20 months, 1 in 18 had detectable measles antibodies (i.e. measles IgG concentration >1.10 immune status ratio), 6 in 17 had detectable antibodies to tetanus (i.e. >0.1 IU/mL) and 14 in 18 had detectable antibodies to *Haemophilus influenzae* type B (Hib) [i.e. >75 ng/mL]. Note that this was a retrospective study and complete data were not available on every patient. Those with undetectable antibodies were re-immunized with measles-mumps-rubella (MMR), diphtheria-tetanus-acellular pertussis (DTaP) (aged <7 years) or diphtheria-tetanus (aged >7 years) and/or Hib conjugate vaccines, according to 'standard immunization practices' (the term 'standard immunization practices' was not defined in the article). After re-immunization, 83% (15 of 18), 91% (10 of 11) and 75% (3 of 4) seroconverted to measles, tetanus and Hib conjugate vaccines, respectively, and antibody titres remained detectable in the majority of patients 1 year after re-immunization.[25]

A booster dose of DTaP administered between 16 to 36 weeks after commencing HAART in 37 children aged 2–9 years who had previously received primary immunization with DTaP and had a negative tetanus antibody titre, generated protective tetanus responses between 4 and 8 weeks after immunization. Rapid antibody decay occurred during the ensuring weeks and by 32 weeks after immunization, only 38% of the children had protective tetanus titres. During the study, there was no increase in adverse events.[26] Additional information was obtained from an analysis of pertussis antibody responses after a single DTaP booster, administered to 92 children aged 2–7 years who had received HAART for a minimum of 3 months. Responses were not compared with those of HIV-uninfected children. The booster dose was well tolerated. Only one child experienced a serious reaction, namely localized erythema and induration. Pertussis antibody titres increased, although they were lower than reported in uninfected children. Pertussis antibody titres were highest in children with pre-HAART CD4+ cell percentages ≥15%. Antibody titres varied inversely with the baseline viral load. Antibody concentrations fell significantly by 24 weeks after immunization, but remained above the pre-booster levels.[27] These studies suggest that, despite good initial responses, a single booster may not be sufficient to sustain protection indefinitely.

Hepatitis B virus (HBV) vaccine is usually administered concurrently with poliomyelitis, diphtheria, tetanus, pertussis and Hib conjugate vaccines. Of 69 HIV-infected children who had previously been immunized with HBV vaccine and subsequently received HAART for a mean duration of 24 months, only one had a protective anti-HBV antibody level (≥10 mIU/mL).[28] Re-immunization of 63 children after a median duration of 31 months on HAART was completed using a three-dose schedule at 0, 2 and 6 months. The major inclusion criteria were (i) age >5 years; (ii) evidence of immune recovery (CD4+ cell percentage >15% for at least 3 months); and (ii) lack of anti-HBV protection. The protective response rates were 17.4% after the first dose, 82.5% after the second dose and 92.1% after the third dose.[29]

The long-term effects of HAART on antibody concentrations against MMR-vaccine strains were described in 59 children with a median age of 4.3 years. Although previously immunized with a single dose of MMR, only 24 of 56 (43%) had protective levels against all three vaccines before HAART was commenced. In children who had measles, mumps and rubella antibodies at the start of HAART, 14 of 35 (40%), 11 of 29 (38%) and 5 of 45

(11%), respectively, lost these antibodies mainly during the first 6 months of HAART. Unanticipated loss of antibodies also occurred in children who had experienced natural varicella-zoster and cytomegalovirus infection, but not in those with antibodies to natural Epstein-Barr virus infection. Risk factors associated with antibody loss were not identified. Fifteen children were given a second dose of MMR during HAART. Of ten children with undetectable measles antibody, six seroconverted, eight of nine with undetectable mumps antibody developed protection, and four of five with undetectable rubella antibody seroconverted.[30]

A recent study provided further insight after MMR re-immunization. HIV-infected children (n = 51) were considered for re-immunization with a single dose of MMR if they (i) were aged >5 years; (ii) had a nadir CD4+ cell percentage <15%; (iii) demonstrated immune recovery (CD4+ cell percentage >15% for >3 months on HAART); and (iv) had no protective antibody levels against measles (anti-measles IgG <320 mIU/mL). Prior to immunization, 51 (100%), 28 (55%) and 11 (22%) children did not have protective antibody to measles, mumps and rubella, respectively. Four weeks after re-immunization, protective antibody concentrations to measles, mumps and rubella were present in 90%, 100% and 78% of the children, respectively. Twenty-four weeks after re-immunization, antibody protection declined to 80%, 94% and 61%, respectively. These antibody responses were not compared with HIV-uninfected children.[31]

### 2.1 Research Considerations

Studies reviewed in this article show that a high proportion of HIV-infected children receiving HAART have inadequate immunity to vaccine-preventable illnesses despite previous routine childhood immunization.[25-31] Low protective coverage rates at the start of HAART, decay of previously induced protective antibody responses during HAART and favourable responses after re-immunization suggest that re-immunization is probably an important intervention for HIV-infected children.

Several unanswered or incompletely answered questions remain, which prevent the formulation of comprehensive programmatic guidelines on re-immunization for resource-constrained countries (table I). First, in published studies, patients were selected for re-immunization depending on baseline vaccine-induced antibody concentrations. It would not be possible to routinely evaluate individual vaccine-specific antibody responses in all HIV-infected children in resource-constrained countries because of limited laboratory and clinical capacity. Instead, the role of routine re-immunization of all HIV-infected children on HAART should be evaluated. Second, the optimal timing of re-immunization in relation to the duration of receiving HAART requires consideration. Generally, children with a CD4+ cell percentage >15% respond more favourably. However, this question requires additional study.[27] Third, should re-immunization be limited to a single booster dose or will greater protective advantage be gained by repeating the primary immunization schedule? Studies described in this article have suggested that primary re-immunization may elicit more favourable antibody responses. Further comparative clinical trials are needed to explore this question.[25-27,29] Fourth, there are no safety and immunogenicity data on the use of whole-cell pertussis vaccine and yellow fever vaccine for re-immunizing children receiving HAART. Whole-cell pertussis vaccine is

**Table I.** Questions relating to re-immunization

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| Routine re-immunization of all HIV-infected children receiving HAART |
| Timing of re-immunization in relation to HAART |
| Re-immunization schedules (i.e. the optimal number of vaccine doses and administration schedules) |
| Clinical effectiveness after re-immunization |
| Durability of protective responses after re-immunization |
| The need for repeat booster doses following re-immunization |
| The role of newer anti-tuberculosis vaccines in re-immunization schedules |
| The safety and effectiveness of pertussis whole-cell vaccine during re-immunization |
| The safety, immunogenicity and effectiveness of yellow fever vaccine during re-immunization |
| Potential theoretical risk of accelerated HIV replication after re-immunization |

**HAART** = highly active antiretroviral therapy.

widely used in resource-constrained countries. It has been shown to be relatively safe in HIV-infected children but should be evaluated in the context of HAART.[32] Fifth, the durability of the immunological response following re-immunization is incompletely studied. Whether additional booster doses are required beyond re-immunization should be established.

## 3. The Role of Additional Vaccines

### 3.1 Pneumococcal Vaccine

In impoverished settings, pneumococcal infection is a leading cause of child mortality. HIV infection increases the risk for pneumococcal infection by 20- to 40-fold.[4] Trials in Africa showed that three doses of a 9-valent pneumococcal conjugate vaccine administered during infancy was highly effective in lowering all-cause mortality and reducing invasive pneumococcal disease significantly in HIV-infected children.[33,34] HIV-infected children demonstrated poorer qualitative antibody responses in response to pneumococcal conjugate vaccine.[9] In a South African trial, vaccine efficacy, measured by specific antibody titres, declined from 65% after 2.3 years to 38.3% after 6 years. This suggested that booster doses are required to maintain protective responses in HIV-infected patients.[35] Pneumococcal conjugate vaccines are also safe and immunogenic in older children. In a study of 225 children aged 2–19 years and who have been stable while receiving HAART for at least 3 months, specific pneumococcal antibody titres were low at study entry, despite 75% of the subjects having previously been immunized with the pneumococcal polysaccharide vaccine. After immunization with two doses of 7-valent pneumococcal conjugate vaccine plus one dose of 23-valent pneumococcal polysaccharide vaccine, 76–96% of the children had antibody titres ≥0.5 μg/mL and 62–88% had antibody titres ≥1.0 μg/mL to five pneumococcal vaccine serotypes. Predictors of high antibody titre responses 24 weeks after immunization included higher pneumococcal antibody concentration at study entry, higher immune status before HAART was commenced, lower viral load at study entry, longer duration of HAART at study entry and age <7 years.[36]

The 23-valent pneumococcal polysaccharide vaccine has been shown to be immunogenic and safe in children aged >2 years who have been treated with HAART. Antibody responses to the polysaccharide vaccine were significantly better in children with a CD4+ cell percentage >25%.[37] In a double-blind randomized clinical trial undertaken among HIV-infected adults in Uganda before HAART was used, the 23-valent vaccine was shown to be ineffective against invasive pneumococcal disease and was associated with increased all-cause pneumonia.[38] Prolonged follow-up of the trial participants confirmed persistent excess of all-cause mortality in the vaccinated group but surprisingly recorded a survival advantage favouring immunization. These results indicate that the use of pneumococcal polysaccharide vaccines in adults remains controversial and warrants further study.[39] Routine childhood immunization with pneumococcal conjugate vaccines should be strongly considered in resource-limited countries. In the interim, the 23-valent, polysaccharide vaccine may have some benefit in preventing invasive pneumococcal disease in HIV-infected children older than 2 years who are receiving HAART.[37]

### 3.2 Rotavirus Vaccine

Rotavirus is the most common cause of severe childhood diarrhoea, precipitating more than 520 000 deaths per annum in developing countries. Current live-attenuated, reassortant vaccines have been evaluated in Europe, North America and Latin America, are safe and may provide up to 100% protection against severe rotavirus diarrhoea and 74–85% protection against any rotavirus infection. Because the protective potential of these vaccines has not been clarified in Africa and Asia, the WHO currently does not recommend global inclusion of rotavirus vaccines in national immunization programmes. In regions where vaccine efficacy has been established, routine immunization is strongly recommended.[40] Several factors may potentially undermine vaccine efficacy in resource-constrained

settings, including young age at onset of rotavirus gastroenteritis, greater rotavirus strain diversity and higher HIV prevalence.[5] HIV infection does not appear to alter the clinical course of rotavirus infection and the associated immunological response. However, safety, immunogenicity and efficacy studies are needed to confirm a role for these vaccines in HIV-infected children.[41]

### 3.3 Influenza Vaccine

Annual influenza immunization using trivalent inactivated vaccines are recommended for HIV-infected children and adults by the WHO.[42] Influenza immunization is advised because HIV-infected individuals (i) are more susceptible to influenza than the general population; (ii) are at an increased risk of mortality due to pneumonia during the influenza season; and (iii) may shed the influenza virus for several weeks or months after an acute episode.[43] Trivalent inactivated vaccines are safe and immunogenic in HIV-infected children and adults. Transient changes in viral load and CD4+ cell count after immunization does not appear to be clinically significant.[42,43] A recently published systematic review showed that influenza vaccines are moderately effective in reducing the incidence of influenza. Four relatively small studies, including only one randomized trial, were used in this analysis. None of these studies included children or data from resource-limited countries.[44]

Although annual immunization coverage is increasing throughout the world, a high proportion of groups at risk of complications from influenza are not immunized. In developing countries, vaccine coverage is believed to be low because of general lack of health infrastructure.[42] In rich countries, vaccine coverage remains sub-optimal. In a study of over 50 000 HIV-infected patients in the US, annual coverage recently reached 41.6%. Patients were more likely to receive influenza vaccine if they were receiving HAART. Vaccine coverage increased with increasing age and the frequency of clinic visits. Those with a CD4+ cell count <200 cells/mm$^3$ and a high viral load were significantly less likely to receive the influenza vaccine.[45]

A recent commentary questioned the evidence base of current recommendations for influenza immunization. According to this analysis, most efficacy studies are of poor methodological quality. Seasonal variability including annual changes in the viral antigenic configuration confounds the interpretation of studies reporting results from one or two influenza seasons. The author called for re-evaluation of the evidence supporting current recommendations.[46] In this regard, the effectiveness of influenza immunization in HIV-infected individuals in Africa remains unclear.

### 3.4 Other Vaccines

The live-attenuated varicella vaccine has been shown to be safe and immunogenic in HIV-infected children with mild or moderate clinical disease or immune suppression. This is currently not a priority vaccine for HIV-infected children in most resource-constrained countries.[47,48] HIV-infected patients are at a higher risk human papilloma virus (HPV)-associated malignancies than the general population. Therefore, newly licensed HPV vaccines for use in young women may be beneficial in this setting. However, results of trials assessing efficacy in HIV-infected populations are not yet available.[49] During the next decade, other vaccine products will require evaluation in HIV-infected populations living in low- and middle-income countries.

## 4. Conclusion

This brief overview identified several limitations of current immunization policy and practice for HIV-infected individuals living in resource-constrained countries. Priority areas that should be addressed include the following: (i) increasing access to early infant HIV testing in resource-constrained countries to permit improved BCG vaccine practice; (ii) development of evidence-based approaches for re-immunizing HIV-infected children who had previously received routine childhood vaccines; (iii) introduction of routine pneumococcal conjugate vaccines for all children in high HIV prevalence settings; (iv) establishment of the role of rotavirus immunization in HIV-infected children; (v) evalua-

tion of the effectiveness of influenza vaccine in HIV-infected children and adults in Africa; and (vi) the impact of HPV vaccines in adult females living in high HIV prevalence settings.

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