

# Vaccines, immunisation and HIV disease

Prakash Jeena, MB ChB, FCP (Paed), Cert in Pulmonology

Department of Paediatrics and Child Health, University of KwaZulu-Natal, Durban

Aspects of immunisation of the HIV-infected person that need to be considered include safety, efficacy with or without highly active antiretroviral therapy (HAART), convenience and relevance to public health. Live attenuated vaccines have been associated with an increased risk of disseminated disease, while killed and subunit vaccines have been shown to be safe. HIV-infected individuals have suboptimal immunological responses to primary vaccination, including memory and protection, and a faster rate of immunological decline of primary vaccine responses. Despite this, there is clear evidence to support vaccination of these individuals as they have a high burden of vaccine-preventable diseases. Immunisation schedules should be universal for all children. Surveillance and monitoring of the vaccinated HIV-infected individual are essential to evaluate responses to and risks associated with vaccination. HAART has a positive effect on rates of response to vaccination.

Human immunodeficiency virus infection almost invariably causes progressive damage to the immune system, characterised by a decline in CD4 T cells. The rate of T-cell decline depends on many factors, including host genetic factors, HI viral load and strain, the developmental stage of the immune system, and host nutrition. HIV infection acquired *in utero* is associated with faster disease progression than infection acquired during delivery or postnatally, as much of the development and maturation of the immune system occurs during the last trimester.<sup>1</sup> The use of highly active antiretroviral therapy (HAART) early in infancy will halt the progression of HIV disease and affect the rate of immunological decay.<sup>2</sup>

Vaccines function through stimulation of the innate and acquired immune systems. Vaccination schedules for HIV-infected infants should be similar to those for non-HIV-infected children (Table I). The administration of whole or split-cell subunits, live attenuated or killed vaccines with or without adjuvant has been associated with antibody or cell-mediated responses that result in sub-clinical infection. HIV-infected individuals have sub-optimal immunological responses to primary vaccination, including memory and protection. This variance cannot be predicted accurately without immunological testing. Studies on vaccine efficacy (seroconversion, immunogenicity and effectiveness), the rate of immunological decline after primary vaccination in HIV-infected infants, and the need for booster doses according to HIV immunological status have not been systematically evaluated.

## Concerns about vaccination

There are currently several concerns about vaccination of HIV-infected individuals. Live attenuated vaccines pose a safety risk to symptomatic HIV-infected children with immune deficiency, and the risk/benefit ratio of these vaccines in HIV-infected individuals with and without HAART needs to be determined. The risk of inducing immune reconstitution inflammatory syndrome (IRIS) must be considered. Post-vaccination surveillance with standardised reporting of efficacy (immunogenicity versus effectiveness) and safety (new, local or systemic adverse effects) is essential.

## Live attenuated vaccines in treated and untreated HIV-infected individuals

Live attenuated vaccines should be avoided in all patients with symptomatic HIV disease, due to safety concerns. In asymptomatic HIV-infected patients these vaccines should be given as early as possible to obtain the best possible immune response before immunological decline. The use of vaccine boosters in patients on HAART is promising but requires further evaluation.

## BCG vaccination

The efficacy of BCG vaccination in HIV-infected individuals is controversial. Efficacy in preventing pulmonary tuberculosis in older children has been variable, with rates between 0% and 80%.<sup>3</sup> In children under 2 years of age the vaccine has protective efficacy of 73% and 75% against tuberculous meningitis and miliary tuberculosis, respectively.<sup>4</sup> With regard to the efficacy of BCG according to HIV status, a study from Rwanda has shown efficacy of 37%, 57% and 70% in HIV-infected, HIV-exposed uninfected and HIV-unexposed uninfected infants, respectively.<sup>5</sup> Against this protective efficacy must be set the changing incidence of congenital tuberculosis in HIV-endemic areas. With the onset of the HIV epidemic, a 10 - 100-fold increase in the incidence of maternal tuberculosis in pregnancy and congenital tuberculosis in newborns has been noted.<sup>6</sup> The increased incidence of congenital tuberculosis may be related to the increased pool of infectious tuberculosis among HIV-infected pregnant women or to the recent claims of possible harm, including death, associated with BCG administration to SIV-infected animals.<sup>7</sup>

The administration of intradermal BCG to infants has been associated with an increase in local and systemic adverse effects with poorer outcomes especially in HIV-infected individuals. Local adverse effects, viz. indurations at the injection site which could last up to 4 - 6 weeks, regional lymphadenitis (<1.5 cm) and formation of pustules that last up to 2 - 3 weeks, are frequently seen (3 000/100 000).<sup>8</sup> Significant local and generalised lymphadenopathy (>1.5 cm in size and >1 non-contiguous site), abscess formation and disseminated BCG-

TABLE I. WHO/UNICEF RECOMMENDATIONS FOR THE IMMUNISATION OF HIV-INFECTED CHILDREN IN DEVELOPING COUNTRIES

Vaccine	Asymptomatic HIV infection	Symptomatic HIV infection or CD 4% <25%	Timing of vaccine
<b>Live vaccines</b>			
BCG	Yes	No	Birth
Measles	Yes	No	6 - 9 mo., booster 18 mo.
MMR	Yes	No	2 doses 4 wks apart >11 mo. of age
Varicella	Yes	No	2 doses 3 mo. apart >11 mo.
Rotavirus	Yes	Unsure	6, 10, 14 wks or 2 doses 10 & 14 wks <7 mo. of age
OPV	Yes	Yes	Birth, 6, 10, 14 wks
Influenza	Yes	No	2 doses 4 wks apart >6 mo.
<b>Killed, subunit/DNA vaccines</b>			
Hepatitis B	Yes	Yes	6, 10, 14 wks
Conjugate pneumococcal vaccine	Yes	Yes	6, 10, 14 wks, booster >2 yrs
<i>Haemophilus influenzae</i>	Yes	Yes	PPV23
Hepatitis B	Yes	Yes	6, 10, 14 wks & booster in 2nd year of life
Diphtheria, whole-cell pertussis, tetanus	Yes	Yes	6, 10, 14 wks - no need for booster
Diphtheria, tetanus	Yes	Yes	6, 10, 14 wks
Diphtheria, acellular pertussis, tetanus	Yes	Yes	18 mo., 5 yrs
Human papillomavirus	Yes	Unsure, probably yes	6, 10, 14 wks & 5 yrs
			3 doses in females before sexual debut between 9 & 12 yrs

osis rarely occur. Aspiration of the regional lymph nodes or abscesses and gastric aspirates has confirmed the presence of BCG strains of *Mycobacterium tuberculosis*. In many instances, these adverse effects have been related to the strain of BCG administered, the method of administration, i.e. intramuscular rather than intradermal, incorrect site of administration or incorrect dose. These adverse reactions, which have been classified into regional, distant, and disseminated effects, are seen in HIV-infected, exposed and uninfected infants and were not associated with increased mortality.<sup>9</sup>

In a recent study from South Africa, the rate of disseminated BCG disease was shown to increase by a dramatic 100-fold, from 0.7 - 30 to 120 - 400/100 000 in a mathematical modelling exercise utilising a retrospective sample of just 17 cases.<sup>10</sup> Disseminated BCG disease was associated with significant mortality and cases were more frequent among HIV-infected individuals. It was postulated that the administration of BCG might contribute to rapid progression of both HIV infection and TB. However, many of these patients had other conditions such as *Pneumocystis jiroveci* pneumonia, cytomegalovirus and acute bacterial infections that were more likely than BCG vaccination to have been responsible for death. Data from Argentina have also suggested an increased risk of disseminated BCG disease, with a risk/benefit ratio attributable to BCG vaccination of 7.8% in HIV-infected infants.<sup>11</sup> Further data with larger sample sizes are urgently required to inform a global policy decision on BCG vaccination. With progressive immunosuppression from HIV disease, there is also a risk of reactivation of latent BCG and development of BCG IRIS.

In South Africa, the current policy of immunising all infants with BCG at birth has not been altered. If, however, BCG is not given to HIV-infected infants before an HIV test result is determined, as per the revised World Health Organization

(WHO) policy for settings where HIV polymerase chain reaction (PCR) testing is available, the overall fall-out rate for BCG vaccination and the incidence of disseminated TB in unvaccinated children should be monitored carefully. BCG should not be given to overtly symptomatic HIV-infected patients of any age, although its use in mildly symptomatic HIV-infected infants and those on HAART needs to be studied.

### Measles vaccination

The immunological response to measles vaccination in HIV-infected infants is unpredictable, with an overall antibody response rate of between 25% and 33%.<sup>12</sup> In severe immune deficiency a seroconversion rate of just 17% has been noted, as opposed to a rate of over 70% in HIV-infected subjects without immune suppression.<sup>13</sup> This is low in comparison with HIV-uninfected infants, in whom seroconversion rates of over 85% have been reported.<sup>14</sup> These responses are worse when the EZ vaccine is administered or if the vaccine recipient is malnourished. As regards immunological decline after primary vaccination, there is more rapid loss of measles-associated antibodies (median time to loss is 3 months) and memory

**Overall, asymptomatic HIV-infected individuals should receive all vaccinations as early as possible.**



cells in HIV-infected than in HIV-uninfected individuals. Consequently, HIV-infected pregnant women have lower levels of measles-specific antibodies to transfer across the placenta to the fetus, placing their newborn infants at increased risk for acquiring measles at an early age. The increased risk of nosocomial transmission of measles virus within health care facilities, the enhanced immunological response to measles vaccination by a healthy immune system prior to the invasion by the HI virus, and the decreased transfer of protective antibodies make a supplemental dose of measles at 6 months of age in HIV-infected infants essential. Better seroconversion rates have been obtained at 6 months than at 9 months. The mortality rate from measles in HIV-infected individuals has been reported to be as high as 40%.<sup>15</sup>

Effective measles eradication programmes have been shown to be successful in preventing the spread of measles in HIV-infected individuals in HIV-endemic areas. Despite a major outbreak of measles in children between 5 and 15 years of age in several of the provinces of South Africa in 2005, HIV-infected patients were not disproportionately affected. The high overall measles immunisation coverage may have prevented the spread of the virus. The WHO policy on measles vaccination in HIV-infected children supports the recommendations of an additional dose of measles vaccine at 6 months with a supplemental dose given during nosocomial outbreaks. A booster dose of measles vaccine 10 - 15 years after initial vaccination, especially in untreated HIV-infected children, is recommended to solve the problem of decline of immunity conferred by vaccination. The immunogenicity of the measles vaccine has been shown to be enhanced during administration of HAART. Measles immunoglobulin is recommended when a severely immunosuppressed HIV-infected child is exposed to measles.

### Measles, mumps and rubella (MMR) vaccination

The MMR vaccine is generally recommended to be given only to patients who are not severely immunocompromised, i.e. CD4 cell count >200 µg/dl or >15%. Two doses are usually recommended, the first after 11 months and the second 4 weeks later. Lower antibody levels (<15 IU/ml) to MMR were seen in HIV-infected and stunted individuals. In rare cases the vaccine has been associated with the acquisition of measles or death in HIV-infected individuals with haemophilia. The use of HAART has been associated with an increased antibody response compared with untreated cases (64% v. 21%).<sup>16</sup> A booster dose of MMR after 5 years produces a substantial antibody response to all components of the vaccine (80%, 90% and 61%, respectively), and this effect is enhanced in children on HAART (83%, 94% and 75%, respectively).<sup>17</sup> No harmful effects of the mumps and rubella components of the vaccine have been reported.

### Poliomyelitis vaccination

Oral polio vaccine (OPV) has a good immunogenic response and is safe in both asymptomatic and symptomatic HIV-infected individuals. Antibody responses of >90% to 3 doses of OPV have been seen in HIV-infected vaccine recipients.<sup>18</sup> Inactivated poliomyelitis vaccine has also been shown to be safe in HIV-infected individuals. There have been only 2 reported cases of vaccine-related paralytic poliomyelitis in HIV-infected patients, although prolonged shedding of the virus makes other susceptible cases vulnerable to infection.

### Influenza vaccination

HIV-infected individuals are at 8-fold greater risk of acquiring influenza-related pneumonia than HIV-uninfected individuals.<sup>19</sup> Administration of the live attenuated influenza vaccine has been associated with an increase in the HIV viral load, so this vaccine is only recommended for use in HIV-infected individuals with CD4 counts of >500/µl. The inactivated influenza vaccine is recommended for all HIV-infected individuals from 6 months of age. It is given once a year, but 2 doses 4 weeks apart are required if it is utilised for the first time in children <9 years of age. Antibody responses are lower in HIV-infected than in uninfected children, and there is no effect on HIV plasma viral load or CD4 count with the inactivated vaccine.

### Varicella vaccination

Varicella and herpes zoster infections are 5-fold commoner in HIV-infected than in uninfected children, especially in those with CD4% <15%. Recurrent varicella disease has been reported in HIV-infected children and adults.<sup>20</sup> Vaccination prevents varicella infection in 82% of patients, and there is a 100% reduction in the incidence of herpes zoster.<sup>21</sup> It is recommended to be given after 11 months in asymptomatic or mildly symptomatic (i.e. CD4 count >500/µl or >25%) HIV-infected children. Two doses given 3 months apart are usually recommended. Administration is not associated with an increase in the HIV viral load. In HIV-infected patients on HAART with a CD4 count <25%, there is a 60% seroconversion rate and an 83% lympho-proliferative response after 2 doses of the vaccine.<sup>22</sup> There is no decrease in burden of varicella infection in HIV-infected patients who are on HAART without being given the varicella vaccine. Non-immunised HIV-infected children who are exposed to chickenpox should be given zoster immunoglobulin within 72 hours of the exposure. Herpes zoster IRIS can occur 2 - 3 months after the onset of HAART.

### Rotavirus vaccination

The safety and efficacy of rotavirus vaccination in HIV-infected individuals is unknown, but research into this matter is currently being conducted.

## Concerns about other vaccine types available for use in HIV-infected children

As a general rule, these vaccines could be given to asymptomatic and symptomatic HIV-infected individuals.

### Conjugated pneumococcal vaccine

The incidence of *Streptococcus pneumoniae* infections is increased 35 - 40-fold in HIV-infected individuals, even those on HAART.<sup>23</sup> The efficacy of the 9-valent pneumococcal conjugate vaccine (PCV) in HIV-infected individuals is 65%, as opposed to 83% in the HIV uninfected. PCV is associated with a 62% decrease in vaccine-related serotypes. Primary immunisation is associated with a 91% seroconversion rate in both symptomatic and asymptomatic HIV-infected treated individuals, but the immunological response declines with time and a booster is therefore necessary.<sup>24</sup> The 23-valent polysaccharide vaccine has a reduced primary immune and



**Live attenuated vaccines  
should be avoided in  
symptomatic HIV-  
infected persons**

long-term memory response but is recommended for use in children >2 years of age. There was, however, an increase in pneumonia in polysaccharide vaccine recipients compared with those who received placebo, due either to replacement disease or destruction of specific B cells.<sup>25</sup> Given the huge burden of pneumococcal disease in HIV-infected children, 3 doses of the conjugated pneumococcal vaccine should be given as early as possible in the first year of life, while a booster dose of the polysaccharide pneumococcal vaccine may be considered after 2 years of age.

### **Haemophilus influenzae type B (HIB) vaccination**

HIV-infected individuals have a 6 - 8-fold increased risk of invasive HIB disease.<sup>26</sup> The initial immunological response in HIV-infected individuals is 54%, as opposed to 90% in the uninfected, and by 15 months there is sequential loss of memory to a protective efficacy of just 30% in the former group.<sup>27</sup> All infants should receive this vaccine as per the Expanded Programme on Immunization (EPI) schedule, with consideration of an additional booster dose in HIV-infected children in the second year of life. Previously unvaccinated older children should receive at least one dose of the conjugated HIB vaccine.

### **Hepatitis B**

Dual infection with hepatitis B and HIV is common. The efficacy of the hepatitis B vaccine in HIV cases is around 50%, dropping to 42% by 13 - 18 months.<sup>28</sup> There is a 3 - 6-fold increased risk of an HIV-infected child becoming a chronic carrier of hepatitis B.<sup>29</sup> If the mother is known to be hepatitis B surface antigen positive during pregnancy, the infant should receive immunoglobulin at birth. The hepatitis B vaccine is recommended to be given to HIV-infected children.

### **Role of DPwT in HIV-infected individuals**

DPwT vaccination (diphtheria, whole-cell pertussis, tetanus) should be given to HIV-infected children according to the routine immunological schedule. The protective antitoxin antibody response rate to 3 doses of DPwT varies between 40% and 100% in symptomatic and asymptomatic HIV-infected children.<sup>30</sup>

### **Human papillomavirus vaccination**

Human papillomavirus (HPV) is a proven potent carcinogen for carcinoma of the cervix. Two types of HPV vaccines are currently registered for prophylaxis against HPV. These vaccines contain no viral DNA capable of replication and are therefore non-infectious, although their safety and efficacy in HIV-infected individuals are largely unknown. Both vaccines have efficacies of over 98% and are extremely safe in HIV-

untested cases. Ideally young girls should be immunised with 3 doses before sexual debut, between 9 and 12 years of age, at 2- to 4-monthly dosing intervals.

## **Conclusions**

Overall, asymptomatic HIV-infected individuals should receive all vaccinations as early as possible to obtain the benefits of a functioning immune system with repeated boosters at as yet undefined times. Live attenuated vaccines should be avoided in symptomatic HIV-infected persons.

## **References**

1. Borkowsky W, Rigaud M, Krasinski, Moore T, Lawrence R, Pollack H. Cell mediated, and humoral immune responses in children infected with human immunodeficiency virus during the first four years of life. *J Pediatr* 1992; 120: 371-375.
2. Melvin AJ, Mohan KM. Response to immunisation with measles, tetanus, and *Haemophilus influenzae* type b vaccines in children who have human immunodeficiency virus type 1 infection and are treated with active antiretroviral therapy. *Pediatrics* 2003; 111: 641-644.
3. Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA* 1994; 271: 698-702.
4. Bourdin Trunz B, Fine PEM, Dye C. Effect of BCG vaccination on childhood tuberculosis meningitis and miliary tuberculosis worldwide; a metanalysis and assessment of cost effectiveness. *Lancet* 2006; 367: 1173-1180.
5. Centers for Disease Control CDC. BCG vaccine and pediatric HIV infection - Rwanda 1988-1990. *MMWR Morb Mortal Wkly Rep* 1991; 40(48): 833-836.
6. Pillay T, Khan M, Moodley J, Adhikari M, Coovadia H. Perinatal tuberculosis and HIV-1: considerations for resource-limited settings. *Lancet Infect Dis* 2004; 4: 155-165.
7. Hesseling AC, Cotton MF, Marais BJ, et al. BCG and HIV reconsidered: Moving the research agenda forward. *Vaccine* 2007; 25: 6565-6568.
8. Jeena PM, Chhagan M, Topley J, Coovadia HM. The safety of the intradermal Copenhagen 1331 BCG vaccine in newborns from Durban, South Africa. *Bull WHO* 2001; 79(4): 337-343.
9. Hesseling AC, Marais BJ, Gie RP, et al. The risk of disseminated Bacille Calmette-Guérin (BCG) disease in HIV infected children. *Vaccine* 2007; 25: 25(11):14-18.
10. Hesseling AC, Rabie H, Marais BJ, et al. Bacille Calmette Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *CID* 2006; 42: 548-557
11. Fallo A, Cerqueiro C, Schargrotsky L, et al. Delayed complications of bacillus Calmette-Guérin (BCG) vaccination in HIV-infected children. Paper presented at the International AIDS Society Conference, Rio de Janeiro, 2005. Abstract 2068.
12. Obaro SK, Pugatch D, Luzuriaga K. Immunogenicity and efficiency of childhood vaccines in HIV-1 infected children. *Lancet Infect Dis* 2004; 4: 510-518.
13. Vaccines preventable deaths and the Global Immunisation Vision and Strategy, 2006-2015. *MMWR Morb Mortal Wkly Rep* 2006; 55(18): 511-515.
14. American Academy of Pediatrics. Measles immunisation in HIV-infected children. *Pediatrics* 1999; 103: 1057-1060.
15. Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. *JAMA* 1992; 267: 1237-1241.
16. Embree JE, Datta P, Stackiw V, et al. Increase risk of early measles in infants of human immunodeficiency virus type-1 seropositive mother. *J Infect Dis* 1992; 165(2): 262-267.
17. Brena AE, Cooper ER, Cabral HJ, Pelton SI. Antibody response to measles and rubella vaccine by children with HIV infection. *J Acquir Immune Defic Syndr* 1993; 6(10): 1125-1129.
18. Supplement to WHO position paper on Poliomyelitis. *World Epidemiological Reviews* 2006; 81: 137-144.
19. Zanetti AR, Amendola A, Besana S, et al. Safety and immunogenicity of influenza vaccination in individuals infected with HIV. *Vaccine* 2002; 20: Suppl 5: B29-32.

# Kindermusik®

a good beginning  
never ends



Backed up with  
**25 years**  
of ongoing research

0 - 18mths  
18mths - 3yrs

3 - 5yrs  
5 - 7yrs

## ENROLL IN 2008

Where music sparks the magical  
development and joy of childhood!  
Kindermusik enhances all therapies!

7 Years of Kindermusik  
(birth to 7 years)  
equips your child  
for 12 years of school!

Exclusive At Home Materials available  
for continuous stimulation. Ask your educator!

Best  
Value  
PER  
CLASS!

**Established in SA for 10 years**

To become a Licensed Kindermusik Educator Contact Kindermusik SA at (018) 468 5143  
or visit [www.kindermusik.co.za](http://www.kindermusik.co.za)

20. Jeena PM, Wesley AG, Coovadia HM. Infectious diseases at the paediatric isolation units. Trends in admission and mortality rates and the early impact of HIV 1994-1996. *S Afr Med J* 1998; 88: 67-72
21. Levin MJ, Gershon AA, Weinberg A, et al. Immunisation of HIV infected children with varicella vaccine. *J Pediatr* 2001; 139: 305-310.
22. Aldeen T, Hay P, Davidson F, Lau R. Herpes zoster infection in HIV-seropositive patients associated with highly active antiretroviral therapy. *AIDS* 1998; 12: 1719-1720.
23. Madhi SA, Kuwanda L, Cutland C, Klugman KP. The impact of the 9-valent pneumococcus vaccine on the public health burden of pneumonia in HIV-infected and uninfected children. *Clin Infect Dis* 2005; 40: 1511-1518.
24. Klugman KP, Madhi SA, Heubner RE, et al. A trial of 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003; 349:1341-1348.
25. AbzugMJ, PeltonSI, Song LY, et al. Immunogenicity, safety, and predictors of response after a pneumococcal conjugate and polysaccharide vaccine series in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatr Infect Dis J* 2006; 25: 920-929.
26. Madhi SA, Petersen K, Huebner RE, et al. Reduced effectiveness of Haemophilus influenzae type B conjugate vaccine in children with a high prevalence of HIV-1 infection. *Pediatr Infect Dis J* 2002; 21: 315-321.
27. Peters VB, Sood SK. Immunity to Haemophilus influenzae type b after re-immunisation with oligosaccharide CRM197 conjugate vaccine in children with human immunodeficiency virus infection. *Pediatr Infect Dis J* 1997; 16: 711-713.
28. Scolfaro C, Fiammengo P, Balbo L, et al. Hepatitis B vaccination in HIV-1 infected children: double efficacy doubling the paediatric dose. *AIDS* 1996; 10: 1169-1170.
29. Whittle H, Jaffar S, Wansbrough M, et al. Observational study of vaccine efficacy 14 years after trial of hepatitis b vaccination in The Gambian children. *BMJ* 2002; 325: 569.
30. Dabbagh A, Eggers R, Cochi S, Dietz V, Strebel P, Cherian T. A global framework for immunisation monitoring and surveillance. *Bull WHO* 2007; 85(12): 904-905.