Do children infected with HIV receiving HAART need to be revaccinated?

Catherine G Sutcliffe, William J Moss

Department of Epidemiology
(C G Sutcliffe PhD, W J Moss MD)
and W Harry Feinstone
Department of Molecular
Microbiology and Immunology
(W J Moss), Bloomberg School
of Public Health, Johns Hopkins
University, Baltimore, MD, USA

Correspondence to:
Dr William J Moss, Department of
Epidemiology, Bloomberg School
of Public Health, Johns Hopkins
University, 615 North Wolfe
Street, Baltimore, MD, USA
wmoss@jhsph.edu

No official recommendations have been made on whether children infected with HIV on highly active antiretroviral therapy (HAART) should be revaccinated. We reviewed published work to establish whether these children have protective immunity to vaccine-preventable diseases and to assess short-term and long-term immune responses to vaccination of children given HAART. In general, children on HAART had low levels of immunity to vaccines given before treatment. Most children on HAART, however, responded to revaccination, although immune reconstitution was not sufficient to ensure long-term immunity for some children. These results suggest that children on HAART would benefit from revaccination, but levels of protective immunity might need to be monitored and some children might need additional vaccine doses to maintain protective immunity. Vaccination policies and strategies for children infected with HIV on HAART should be developed in regions of high HIV prevalence to ensure adequate individual and population immunity.

Introduction

As part of the Expanded Programme on Immunization (EPI), WHO recommends giving routine childhood vaccines to children infected with HIV,[1] with the exceptions of BCG vaccine to infants with confirmed HIV infection and measles vaccine to severely immunosuppressed children.[2,3] However, because of the progressive effects of HIV infection on the ability of the immune system to mount an effective response, many infected children have poorer responses to vaccines than do uninfected children.[4] In general, fewer children infected with HIV achieve protective immunity, and those who do might experience greater and more rapid waning of immunity.[4,5]

Highly active antiretroviral therapy (HAART) is effective in reducing morbidity and mortality in children infected with HIV by suppressing viral replication and restoring immune function.[6–10] However, immune reconstitution in children is primarily through the generation of naive T cells rather than expansion of memory T cells, as in adults.[11–13] Consequently, HAART might not restore vaccine-induced immunity established before the start of therapy. No recommendations have been issued on whether children infected with HIV on HAART should be revaccinated.

In low-income and middle-income countries, particularly those in sub-Saharan Africa that bear the greatest burden of HIV infection in children,[14] antiretroviral treatment programmes have been scaled-up substantially, increasing access to life-prolonging treatment for children infected with HIV.[15] However, these children often access treatment at a later stage in disease progression and at older ages than in more developed countries,[16,17] and will have received routine immunisations before treatment. As a result, revaccination might be important to ensure protection. In countries heavily affected by the HIV epidemic, children receiving HAART who remain susceptible to infection could become sufficiently numerous to sustain transmission of vaccine-preventable diseases and jeopardise control efforts.[18]

We reviewed published work (table 1)[12,19–55] to establish whether children taking HAART have protective immunity to vaccine-preventable diseases and to explore short-term (≤3 months) and long-term (>3 months) immune responses to immunisation. The implications of these findings for revaccination of children infected with HIV on HAART are discussed.

Studies of vaccines and HAART

We identified 38 studies that addressed at least one of the questions of interest (table 1). For the question of whether children taking HAART have protective immunity to vaccine-preventable diseases, studies were included if children were vaccinated before being started on HAART and measures of immunity were reported after the start of HAART but before revaccination. Studies of influenza were not included for this question because vaccine-induced immune responses could not be distinguished from those due to infection. For questions about the short-term (≤3 months) and the long-term (>3 months) immune response to vaccination on HAART, studies were included if children were revaccinated or received new vaccines to which they had no prior exposure after being started on HAART and either short-term or long-term immune responses were measured.

Immunity to vaccine-preventable diseases
Non-replicating vaccines

For non-replicating vaccines, including diphtheria tetanus pertussis vaccine (DTP), hepatitis B vaccine (HBV), pneumococcal vaccines, and conjugate *Haemophilus influenzae* type b vaccines (Hib), the proportion of children with an immune response, as defined by each study, after being started on HAART was highly variable, with no clear trend by type of vaccine (table 2). The proportion of children with an immune response after being started on HAART ranged from 38% to 77% for tetanus, 40% to 65% for diphtheria, 1% to 100% for HBV, and 25% to 87% by serotype for pneumococcal vaccines. The duration of HAART at the time antibody concentration was measured varied, with the average duration ranging from 28 weeks to 5·3 years.

	Vaccine	Number taking HAART/total	Age at study entry (years)	CD4 status at study entry	Question addressed in study*
Non-replicating vaccines					
Blazevic, 2001[19]	TT	11/11	Median 11·1; range 7·4–18·4	Median 598 cells per µL; range 63–835	A
Hainaut, 2003[20]	TT	19/19	Median 5·6; range 0·6–17·2	89% in CDC immune categories 2 and 3	A
Vigano, 2000[12]	TT	25/25	Median 9·7–9·8 by CDC stage	Median 5–27% by CDC stage	A
Peruzzi, 2002[21]	TT	7/7	Median 10·4; range 7·1–14·1	Range 15–42%	A
Ghosh, 2009[22]	TT	9/9	Not specified (mean 9·36 [SD 4·15] among full cohort)	Mean ARP 68·9	A, B
Essajee, 1999[23]	DT	25/25	Median 8·95; range 1·87–17·53	Median 2·0%; range 0–6	A, B
Rosenblatt, 2005[24]	DTaP	37/37	Median 6·1; range 2·9–10·9	Median 34%; range 14–51	B, C
Abzug, 2007[25]	DTaP	92/92	Median 9·3	Median 33%	B, C
Ching, 2007[26]	TT	15/15	Median 12·6	CR: median 35%; ICR: median 26%	A, B, C
Luzuriaga, 2000[27]	TT	17/17	Mean 1·9; range 0·5–3·0	Mean 41%; range 14–57%	B
Rigaud, 2008[28]	DTP, HAV	46/46	Median 13; range 3–17	Median 7%; range 1–14	A, B, C
Tangsinmankong, 2004[29]	Pneumococcus	41/41	Range 2–15; 39% between 2 and 6	Mean 31·9%; SD 10·2%	B
Tarrago, 2005[30]	Pneumococcus	56/56	Median 11; range 3–19	Median 29%	A, B
Costa, 2008[31]	Pneumococcus	38/40	Range 2–9	95% with CD4% ≥25%	A, B
Abzug, 2006[32]	Pneumococcus	225/225	Median 9·6	Median 33%	A, B, C
Fernandes, 2008[33]	HBV	42/58	Median 7; range 1·5–12	Mean 831 cells per µL; SD 604	A
Siriaksorn, 2006[34]	HBV	75/75	Mean 9·6; SD 2·5	Mean 25%; SD 5	A
Lao-araya, 2007[35]	HBV	63/63	Mean 10·1; SD 2·4	Mean 27·2%; SD 6·7	B
Pippi, 2008[36]	HBV	47/84	Median 4·7; 95% CI 4·2–5·2	40·4% in CDC category 1	C
Abzug, 2009[37]	HBV	204/204	Median 9·1	Median 34%	A, B, C
Weinberg, 2006[38] Weinberg, 2009[39]	HAV	152/152	Median 9·2	Median 32%	B, C
Siberry, 2008[40]	HAV	83/84	37% ≥13	65% with CD4% ≥25%	C
Tanzi, 2006[41]	Influenza	29/29	Mean 10·3: SD 4·3	83% had CD4 >500 cells per µL	B
Montoya, 2007[42]	Influenza	16/16	Mean 4·6; SD 2·5	Mean 1202 cells per µL; STD 844	B
Vigano, 2008[43]	Influenza	24/24	Mean 12·6; SD 4·6	Mean 36·9%; SD 9·1	B, C
Replicating vaccines					
Aurpibul, 2006[44]	MMR	93/93	Mean 9·7; SD 2·6	Mean 24·7%; SD 4·8	A
Berkelhamer, 2001[45]	MMR	14/28	Range 2·2–11	Range 10–45%	B
Lima, 2004[46]	MMR	15/15	Median 15·4; range 12·4–17·6	Median 1781 cells per µL; range 690–5137	B
Aurpibul, 2007[47]	MMR	51/51	Mean 10·2; SD 2·5	Mean 27·2%; SD 5·7	B
Bekker, 2006[48]	MMR	59/59	Median 4·3; IQR 1·4–8·8	..	A, C
Levin, 2006[49]	VZV	17/17	Median 6·2; 95% CI 3·3–6·7	Median 38%; 95% CI 34–48	B, C
King, 2001[50]	Influenza	24/24	Mean 4·7; range 1–7·9	79% CDC class 1	B
Both replicating and non-replicating vaccines					
Zaccarelli-Filho, 2007[51]	DTP, MMR, HBV	41/41	Good VLR:† mean 10·9; SD 3·3 Partial VLR: mean 7·4; SD 3·1 Poor VLR: mean 9·4; SD 3·9	Good VLR: median 33·0% Partial VLR: median 26·4% Poor VLR: median 21·6%	A
Farquhar, 2009[52]	TT, MMR	90/90	Median 4·9; IQR 2·6–6·5	Median 6·3%; IQR 3·0–10·6	A, B
Pensieroso, 2009[53]	TT, MMR, pneumococcus	64/70	Early:‡ mean 6·8; SD 3·2 Late control: mean 13·7; SD 4·1 Late failure: mean 15·8; SD 4·1	Early: median 35% Late control: median 33% Late failure: median 22%	C
Levin, 2008[54]	Influenza	243/243	LAIV: mean 11·4; SD 3·3 TIV: mean 11·9; SD 3·0	LAIV: mean 33·2%; SD 8·4 TIV: mean 34·1%; SD 8·1	B, C
Melvin, 2003[55]	DTP, MMR, Hib	19/19	Median 7; range 3–14	Median 26%; range 1–41	B, C

TT=tetanus toxoid. ARP=age-related percentage of peripheral blood CD4 T cells compared with CD4 T cells of healthy children. DT=diphtheria and tetanus. DTaP=diphtheria, tetanus, and acellular pertussis vaccine. CR=complete responder (patients with undetectable plasma HIV-RNA [≤2·6 log copies per mL] for at least 2 years before TT booster). ICR=incomplete responder (no change or increase in HIV plasma viraemia despite HAART). DTP=diphtheria, tetanus, and pertussis vaccine. HAV=hepatitis A virus vaccine. HBV=hepatitis B virus vaccine. MMR=measles, mumps, and rubella vaccine. VZV=varicella zoster virus vaccine. Hib=*Haemophilus influenzae* type B vaccine. VLR=viral load responder. LAIV=live attenuated influenza vaccine. TIV=inactivated trivalent influenza vaccine. *A: Do children taking HAART have protective immunity to vaccine-preventable diseases? B: What is the short-term (≤3 months) immune response to vaccination on HAART? C: What is the long-term (>3 months) immune response to vaccination on HAART? †Good VLRs are patients with HIV-RNA below 400 copies per mL for at least 12 months before tests. Partial VLRs are patients who showed at least 1 log₁₀ reduction in HIV-RNA copies per mL after HAART initiation. Poor VLRs are patients who showed a decrease of <1 log₁₀ of HIV-RNA copies per mL after being started on HAART. ‡Early: children who started HAART within the first year of life. Late control: children who were started on HAART after 1 year of age who achieved viral suppression. Late failure: children who were started on HAART after 1 year of age who did not achieve viral suppression.

Table 1: Description of studies evaluating immunity to vaccine-preventable diseases among children in receipt of HAART

Antibody concentrations defining an immune response were not consistent for each vaccine (table 2), further complicating comparisons.

Two studies were designed specifically to investigate the effect of HAART on immunity to vaccine-preventable diseases and reported antibody concentrations for tetanus

	Time on HAART	Assay used	Pre-HAART antibody measure	Post-HAART antibody measure	Definition of immune response
Non-replicating vaccines					
Tetanus					
Zaccarelli-Filho, 2007[51]	Good VLR:* mean 4·6 years (SD 1·0) Partial VLR: 3·7 (1·1) Poor VLR: 4·4 (1·0)	Double antigen ELISA	..	Good VLR: 71% protected Partial VLR: 77% protected Poor VLR: 73% protected	>0·1 IU/mL
Rigaud, 2008[28]	28 weeks	IgG ELISA kit	..	55% responded	>0·1 IU/mL
Ching, 2007[26]	Median 5·3 years; range 1·4–6·2	IgG EIA	..	38% protected	≥0·15 IU/ml
Farquhar, 2009[52]	6 months	In-house ELISA	78% positive	59% positive overall 31% of positives seroreverted 23% of negatives seroconverted	>0·01 IU/mL
Ghosh, 2009[22]	36 months (SD 20·2)	ELISA	Mean 0·25 IE/mL (SD 0·3)	Mean 0·67 IE/mL (SD 0·9)	
Diphtheria					
Zaccarelli-Filho, 2007[51]	Good VLR: mean 4·6 (SD 1·0) Partial VLR: 3·7 (1·1) Poor VLR: 4·4 (1·0)	Double antigen ELISA	..	Good VLR: 65% protected Partial VLR: 61% protected Poor VLR: 40% protected	>0·1 IU/mL
Hepatitis B virus					
Fernandes, 2008[33]	Median: 53 months; range 4–118	ELISA	..	17% protected	≥10mIU/mL
Zaccarelli-Filho, 2007[51]	Good VLR: mean 4·6 (SD 1·0) Partial VLR: 3·7 (1·1) Poor VLR: 4·4 (1·0)	ELISA	..	Good VLR: 100% protected Partial VLR: 100% protected Poor VLR: 91% protected	>10mIU/mL
Siriaksorn, 2006[34]	Mean 24 months (SD 4·4)	ELISA	..	1% protected	≥10mIU/mL
Abzug, 2009[37]	≥6 months	ETI-AB-AUK PLUS immunoassay	..	24% seropositive	≥10mIU/mL
Pneumococcus (PPV)					
Abzug, 2006[32]†	≥6 months	ELISA	..	31% responded (serotype 1), 58% (6B), 35% (14), 87% (19F), 25% (23F)	≥0·5 µg/mL
Costa, 2008[31]†	..	ELISA	..	Mean 0·343 ug/mL (serotype 4), 0·751 (6B), 0·453 (9V), 0·935 (14), 0·509 (18C), 1·513 (19F), 0·517 (23F)	
Tarrago, 2005[30]	..	ELISA	..	Mean 0·4 ug/mL (SD 0·8; serotype 6B); 1·3 (2·4; 14); 1·2 (4·0; 23F)	
Replicating vaccines					
Measles					
Farquhar, 2009[52]	6 months	ELISA	33% positive	42% positive overall 53% of positives seroreverted 40% of negatives seroconverted	>1·1 antibody index
Zaccarelli-Filho, 2007[51]	Good VLR: Mean 4·6 (SD 1·0) Partial VLR: 3·7 (1·1) Poor VLR: 4·4 (1·0)	Indirect ELISA	..	Good VLR: 43% protected Partial VLR: 44% protected Poor VLR: 45% protected	>0·12 IU/mL
Aurpibul, 2006[44]	Mean 24·5 months (SD 4·1)	ELISA	..	42% protected	≥320 mIU/mL
Bekker, 2006[48]	Median 205 weeks; IQR 124–359	Enzyme immunoassay	63% positive	40% of positives lost protective antibodies	≥9·0 AU/mL
Mumps					
Bekker, 2006[48]	Median 205 weeks; IQR 124–359	Enzyme immunoassay	52% positive	38% of positives lost protective antibodies	≥9·0 AU/mL
Rubella					
Bekker, 2006[48]	Median 205 weeks; IQR 124–359	Enzyme immunoassay	80% positive	11% of positives lost protective antibodies	≥10·0 IU/mL
Zaccarelli-Filho, 2007[51]	Good VLR: mean 4·6 (SD 1·0) Partial VLR: 3·7 (1·1) Poor VLR: 4·4 (1·0)	Indirect ELISA	..	Good VLR: 43% protected Partial VLR: 66% protected Poor VLR: 27% protected	>10·0 IU/mL

VLR=viral load responder. IU=international units. IE=internationale einheit. PPV=pneumococcal polysaccharide vaccine. AU=antibody units. *Good VLRs are patients with HIV-RNA below 400 copies per mL for at least 12 months before tests. Partial VLRs are patients who showed at least 1 log₁₀ reduction in HIV-RNA copies per mL after being started on HAART. Poor VLRs are patients who showed a decrease of <1 log₁₀ of HIV-RNA copies per mL after being started on HAART. †The study by Abzug and colleagues[32] included 25% who had not previously received pneumococcal polysaccharide or conjugate vaccine. The study by Costa and colleagues[31] included 40% who had not previously received pneumococcal polysaccharide vaccine.

Table 2: **Studies reporting humoral immunity to vaccine-preventable diseases after the start of HAART**

toxoid before and after initiation of HAART.[22,52] In the study by Farquhar and colleagues from Kenya,[52] 78% of children were seropositive before taking HAART. After 6 months of treatment, only 59% of children were seropositive, with 23% of children who were seronegative before HAART becoming seropositive after. Unexpectedly, 31% of children who were seropositive before HAART reverted to being seronegative after. In the study by Ghosh and colleagues from Germany,[22] mean antibody concentration rose from 0·25 IE/mL (SD 0·3) before HAART to 0·67 IE/mL (SD 0·9) after a mean of 36 months on HAART.

Predictors of immune response after starting HAART were reported in several studies.[25,32,37,51,52] Most studies assessed demographic characteristics as well as immunological and virological variables, including nadir values and values since starting HAART, in relation to immune responses to vaccines. Virological and immunological measurements at other potentially important times, such as the time of first vaccination, were not available in any of the studies. For tetanus toxoid, older age when starting HAART and greater increase in the proportion of CD4 T cells between start and 6 months of treatment were positively associated with an immune response after HAART in one study,[52] although the proportion of CD4 T cells, HIV-1 viral load, and anthropometric measures at the start of HAART were not associated with immunity.[52] Additionally, young age was associated with loss of immunity after being started on HAART. In another study, HAART response measured by viral suppression was not associated with immunity to tetanus toxoid.[51] For diphtheria and HBV, one study[51] found that children with good or partial responses to HAART, defined by long-term suppression of HIV-1 viral load, were more likely to have immunity than were children with poor responses to HAART, although this result was not statistically significant. In another study of HBV,[37] better immune status, defined by both pre-HAART nadir and study entry (after HAART) proportions of CD4 T cells, and shorter time between previous HBV vaccination and study entry were positively associated with immune response to HBV. When the components of immune status were examined, nadir proportions of CD4 T cells were more predictive than were those of CD4 T cells at study entry. For pneumococcal vaccines, immune status, as previously defined for HBV, was not predictive of immunity. Age, race, sex, duration of current HAART regimen, pre-HAART nadir proportions of CD4 T cells, and proportions of CD4 T cells and HIV-1 viral load at study entry (after HAART) were predictive for at most one serotype.[32]

Lymphoproliferative responses before and after initiation of HAART also were investigated for tetanus toxoid.[12,19–23,26,28] Responses before HAART ranged from 0% to 28% of children who had a stimulation index (SI) of either ≥3 or >4. Responses after HAART ranged from 0% to 71%. Four studies reported an increase in the proportion of children responding,[12,21,22,28] one study noted no change

in response,[19] and two studies reported a decrease in lymphoproliferative responses after HAART.[20,23]

Several studies compared the immune responses of children infected with HIV taking HAART with control groups (figure). In the study by Ching and colleagues from the USA,[26] antibody concentrations and lymphoproliferative responses to tetanus toxoid among children infected with HIV receiving HAART were compared with those of healthy adults. Healthy adults were more likely to have protective antibody concentrations (100% vs 38%) and lymphoproliferative responses (100% vs 7%). In studies by Blazevic and colleagues[19] and Peruzzi and colleagues[21] adults and children not infected with HIV had higher lymphoproliferative responses (100% vs 11%)[19] to tetanus toxoid. In a study by Fernandes and colleagues,[33] HBV antibody concentrations in children with HIV who were receiving HAART were compared with those of children not receiving HAART (most of whom were receiving only two antiretroviral drugs) and healthy, uninfected, age and sex matched children.[33] Compared with children receiving HAART, infected children not receiving HAART (44% vs 17%) and uninfected children (87% vs 17%) were more likely to be seropositive for HBV. Differences due to HAART in children infected with HIV were postulated to be due to greater decline in CD4 T cells and immune function among children on HAART.

Live viral vaccines
For measles mumps rubella vaccine (MMR), the proportion of children with an immune response, as defined by each study, after starting HAART ranged from 42% to 45% for measles virus and 27% to 66% for rubella virus (table 2). Two studies reported antibody concentrations before and after HAART. For measles, the proportion of Kenyan children who were seropositive increased from 33% before HAART to 42% after HAART.[52] However, 53% of children who were seropositive before HAART lost protective immunity, whereas 40% of children who were seronegative or had borderline antibody concentrations became seropositive after receiving HAART for 6 months. In the study by Bekker and colleagues,[48] 63% of children were seropositive for measles before HAART, but 40% became seronegative after a median of 205 weeks on HAART. Similarly, 52% of children were seropositive for mumps before HAART and 80% for rubella, but 38% and 11% became seronegative after starting HAART.[48]

Predictors of immune responses for children on HAART were assessed in four studies, with few consistent results. For measles, lower HIV-1 viral load before HAART was predictive of an immune response after HAART in one study[52] but not another,[44] and HAART response (defined by long-term suppression of viral load) or viral load after HAART were not predictive of response in any study.[44,51,52] Higher proportions of CD4 T cells after HAART were marginally associated with an immune response in one study[52] but not another,[44] and the proportion of CD4 T
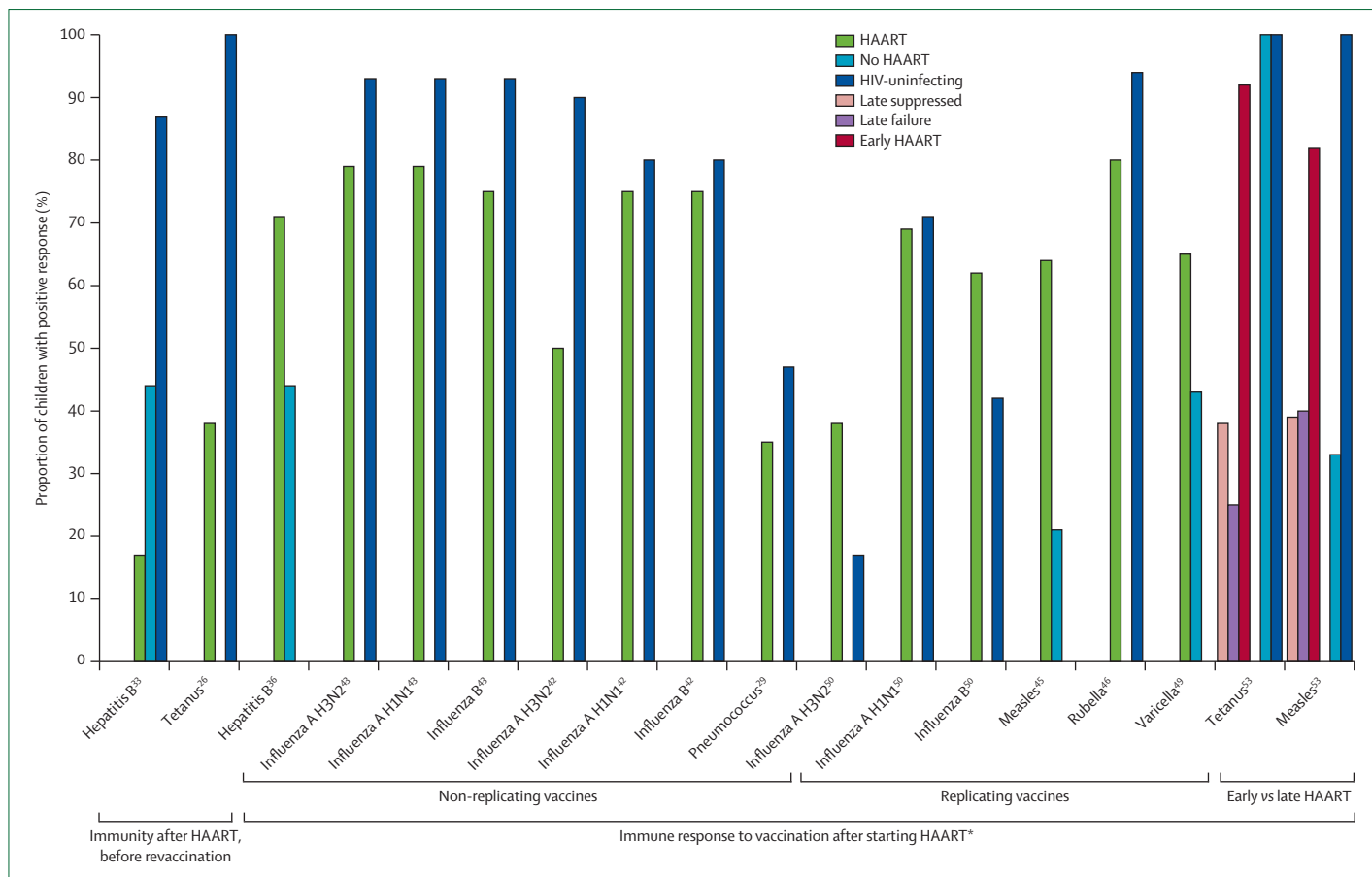
Figure: Comparison of immune responses to vaccination between children infected with HIV on HAART and control groups

Late suppressed=children who were started on HAART after age 1 year in whom viral suppression was achieved. Late failure=children who were started on HAART after age 1 year in whom viral suppression was not achieved. Early HAART=children who were started on HAART within the first year of life. HAART=all children on HAART. No HAART=children infected with HIV who either had no history of HAART or were not in receipt of HAART. HIV-uninfected=children in the HIV-uninfected control group. *Children may have received new vaccines or may have been revaccinated with prior vaccines.

cells before HAART was not predictive of response in either study.[44,52] Clinical status, either by Centers for Disease Control and Prevention (CDC) clinical category or anthropometric measures, was not predictive of immune response to measles vaccine.[44,52] Age at study enrolment was not predictive of immune response in several studies,[44,52] but younger age was associated with loss of immunity to measles virus in another.[48] For rubella, children with a good or partial response to HAART, defined by long-term viral suppression, were more likely to have protective immunity, although this difference was not statistically significant.[51] For measles, mumps, and rubella, low pre-HAART antibody concentrations were predictive of loss of immunity, although this finding was statistically significant only for measles and rubella.[48,52]

Response to vaccination after HAART
Non-replicating vaccines
Studies of DTP, conjugate Hib, HBV, pneumococcal, and inactivated influenza vaccines involved revaccination of children on HAART who had previously received the

same vaccines before starting HAART (table 3). Within the first 3 months after revaccination, the proportion of children responding to vaccination, as defined by each study, was 53–100% for tetanus toxoid,[24,26–28,52,55] 75% for conjugate Hib vaccine,[55] 46–92% for HBV vaccine,[35,37] 29–96% by serotype for pneumococcal vaccine,[29–32] and 50–100% by strain for influenza vaccine.[41–43,54] By contrast, studies of HAV involved vaccination of children for the first time after starting HAART, and 72–97% of children responded after receiving 2–3 doses.[28,38]

Several studies followed children after vaccination to evaluate the degree of waning immunity among children receiving HAART (table 3). In general, immunity declined but a high proportion of children maintained immunity about a year after vaccination. For tetanus toxoid, one study from the USA[24] reported a decline from 74% seropositive at 4 weeks to 38% by 32 weeks after vaccination,[24] although in three other studies 85–90% of children maintained immunity 1 year after vaccination.[26,28,55] For pertussis, antibody concentration declined from 22·3 EU/mL at 8 weeks to 10·1 EU/mL by 48 weeks and

6·8 EU/mL by 96 weeks after vaccination.[25] For Hib, three (75%) children had detectable antibodies 4 weeks after vaccination and two (100%) at 52 weeks.[55] For HBV, the proportion of seropositive children decreased from 46% 8 weeks after revaccination to 38% after 96 weeks and 25% after a median of 4·6 years.[37] All children remaining in the study after a median of 4·6 years were revaccinated a second time. Of the children who were seronegative within 1 week of the second revaccination, 37% seroconverted 4 weeks after vaccination. For influenza, protective responses tended to be lower for influenza B virus and decreased over time for all strains.[42,43,54] One

	Vaccine (number of doses)	Assay used; definition of immune response	New vaccine?*	Time after vaccination (short-term); response	Time after vaccination (long-term); response
Non-replicating vaccines					
Tetanus					
Melvin[55]	Tripedia or DT (one)	EIA; >0·1 IU/mL	No	4 weeks; 90% detectable	52 weeks; 86% detectable
Rigaud[28]	DTaP or Td or DT (three)	ELISA; >0·1 IU/mL	No	4 weeks after third dose; 94% responded	52 weeks after third dose; 90% responded
Ching[26]	Tetanus (one)	IgG EIA; ≥0·15 IU/mL	No	Median 2·3 months; 92% responded	Median 11·8 months; 85% responded
Farquhar[52]	TT (one)	ELISA; >0·01 IU/mL	No	4 weeks; 75% positive	..
Rosenblatt[24]	DTaP (one)	Red blood cell agglutination assay; Reciprocal titer >243	No	4 weeks; 74% positive 8 weeks; 67% positive 18 weeks; 53% positive	32 weeks; 38% positive
Ghosh[22]	TT (one)	ELISA; ..	No	After booster; mean 3·3 IE/mL (SD 1·8)	..
Pensieroso[53]	Hexavac or Infanrix-hexa plus Boosterix (..)	ELISA; >0·15 units/mL	..	..	Early:† mean 5·3 years; 92% protected Late control: mean 7·4 years; 38% protected Late failure: mean 9·7 years; 25% protected
Rigaud[28]	DTaP or Td or DT (three)	LPA; SI >3	No	4 weeks after third dose; 73% responded	52 weeks after third dose; 61% responded
Ching[26]	Tetanus (one)	LPA; SI >3	No	Median 2·3 months; 47% responded	..
Essajee[23]	DT (one)	LPA; SI ≥3	No	1–2 months; 67% positive	..
Ghosh[22]	TT (one)	LPA; SI ≥3	No	After booster; 86% response	..
Luzuriaga[27]	TT (..)	LPA; SI ≥3	No	LPA closest to 16 months of age; 100%	..
Diphtheria					
Essajee[23]	DT (one to two)	LPA; SI ≥3	No	1–2 months; 17% positive	..
Pertussis					
Abzug[25]	Infanrix (one)	ELISA; ..	No	8 weeks; mean 22·3 EU/mL, 95% CI 15·9–31·2	48 weeks; 10·1 EU/mL, 95% CI 7·1–14·4 96 weeks; 6·8 EU/mL, 95% CI 5·1–9·1
Haemophilus influenzae					
Melvin[55]	HibTiter (one)	EIA; >75 ng/mL	No	4 weeks; 75% detectable	52 weeks; 100% detectable
Hepatitis A virus					
Rigaud[28]	Havrix (three)	Quantitative ELISA; ≥20 mIU/mL	Yes	4 weeks after third dose; 72% responded	52 weeks after third dose; 66% responded
Siberry[40]	Havrix or Vaqta (one to two)	Microparticle EIA; ..	Yes	..	Median 42 weeks; 85% seropositive
Weinberg[38]	Havrix (two)	ELISA; ≥20 mIU/mL	Yes	8 weeks after second dose; 97% protected	18 months after second dose; 90% protected
Rigaud[28]	Havrix (three)	LPA; SI >3	Yes	4 weeks after third dose; 12% responded	52 weeks after third dose; 13% responded
Hepatitis B virus					
Pippi[36]	HBVAXPRO (three)	ELISA; ≥10 mIU/mL	..	..	5 months after third dose; 71% protected
Lao-araya[35]	HBV (three)	ELISA; ≥10 mIU/mL	No	2 months after first dose; 17% protected 4 months after second dose; 83% protected 1 month after third dose; 92% protected	..
Abzug[37]	Recombivax HB (one)	ETI-AB-AUK PLUS immunoassay; ≥10 mIU/mL	No	8 weeks; 46% seropositive	48 weeks; 38% seropositive 96 weeks; 38% seropositive Median 4·6 years; 25% seropositive
Influenza virus					
Tanzi[41]	Inflexal V (one)	HAI; ≥1:40	No (66% had prior vaccine)	30 and 90 days; A H1N1 100% protected, A H3N2 100%, B 76% at both time points	..
Montoya[42]	Imovax Gripe (one)	HAI; ≥1:40	..	1 month; A H1N1 75% protected, A H3N2 50%, B 56%	..
Vigano[43]	Inflexal V (one)	HAI; ≥1:40	Yes	1 month; A H1N1 79% protected, A H3N2 79%, B 75%	6 months; A H1N1 75%, A H3N2 54%, B 63%
Levin[54]	FluZone (one)	HAI; titre ≥40	No (prior TIV)	1 month; A H1N1 67% protected, A H3N2 96%, B 69%	6 months; A H1N1 55%, A H3N2 97%, B 63%

(Continues on next page)

	Vaccine (number of doses)	Assay used; definition of immune response	New vaccine?*	Time after vaccination (short-term); response	Time after vaccination (long-term); response
(Continued from previous page)					
Pneumococcus					
Tangsinmankong[29]	Pneumovax 23 (one)	ELISA; clinical protection‡	..	1–3 months; 35% protected	
Pensieroso[53]	Pneumo 23 (..)	ELISA; ..	..	..	Early: mean 3·8 years; med 95 IU/mL§ Late control: mean 3·8 years; med 50 IU/mL Late failure: mean 3·9 years; med 25 IU/mL
Tarrago[30]	Prev(e)nar (two)	ELISA/OPA; ≥2-fold increase in ELISA/OPA	No (prior PPV)	3 months after second dose; 44% responded (serotype 6B), 29% (14), 38% (24F)	..
Costa[31]	PCV-7 (two)	ELISA; ≥1·3 ug/mL	No (60% had prior PPV)	1–3 months after second dose; 65% responded to ≥4 serotypes (45% [serotype 4], 55% [6B], 58% [9V], 90% [14], 70% [18C], 80% [19F], 50% [23F])	..
Abzug[32]	Prevnar (2)+PNU-IMUNE 23 (one)	ELISA; ≥0·5ug/ml	No (75% had prior PPV)	8 weeks after third dose; 81% responded (serotype 1), 92% (6B), 92% (14), 96% (19F), 76% (24F)	80 weeks after third dose; 75% (serotype 1), 92% (6B), 88% (14), 95% (19F), 74% (24F)
Replicating vaccines					
Measles					
Melvin[55]	M-M-R II (one)	EIA; >1·10 ISR	No	4 weeks; 83% detectable	52 weeks; 73% detectable
Berkelhamer[45]	MMR (one)	ELFA; ≥0·7	No	1–4 months; 64% positive	..
Pensieroso[53]	Priorix (..)	ELISA; >0·2 units/mL	..	..	Early: mean 4·2 years; 82% protected Late control: mean 4·7 years; 39% protected Late failure: mean 3·7 years; 40% protected
Farquhar[52]	Measles (one)	ELISA; >1·1 antibody index	No	4 weeks; 78% positive	..
Aurpibul[47]	Priorix (one)	ELISA; ≥320 mIU/mL	No	4 weeks; 90% protected; 24 weeks; 80% protected	..
Bekker[48]	MMR (one)	EIA; ≥9·0 AU/mL	No	..	Median 48 weeks, IQR 19–93; 60% of negatives seroconverted
Mumps					
Bekker[48]	MMR (one)	EIA; ≥9·0 AU/mL	No	..	Median 48 weeks, IQR 19–93; 89% of negatives seroconverted
Aurpibul[47]	Priorix (one)	ELISA; titre >1:500	No	4 weeks; 78% protected; 24 weeks; 61% protected	..
Rubella					
Bekker[48]	MMR (one)	EIA; ≥10·0 IU/mL	No	..	Median 48 weeks, IQR 19–93; 80% of negatives seroconverted
Aurpibul[47]	Priorix (one)	ELISA; ≥10 mIU/mL	No	4 weeks; 100% protected; 24 weeks; 94% protected	..
Lima[46]	MMR (one)	ELISA; >10 IU/mL	Yes	3 months; 80% protected	..
Varicella zoster virus					
Levin[49]	Oka/Merck vaccine (two)	FAMA; titre ≥1:2	Yes	20 weeks (8 weeks after second dose); 71% positive	52 weeks; 65% positive 104 weeks; 47% positive 156 weeks; 38% positive
Levin[49]	Oka/Merck vaccine (two)	LPA; SI ≥3	Yes	20 weeks (8 weeks after second dose); 85% positive	52 weeks; 92% positive 104 weeks; 85% positive 156 weeks; 33% positive
Influenza virus					
King[50]	LAIV by Aviron (two)	HAI; ≥4-fold increase	..	28–70 days after first dose; 59% seroresponse to ≥1 strain (A H1N1 41%, A H3N2 32%, B 45%) 28–35 days after second dose; 77% seroresponse to ≥1 strain (A H1N1 69%, A H3N2 38%, B 62%)	..
Levin[54]	FluMist (one)	HAI; titre ≥40	No (prior TIV)	1 month; A H1N1 63% protected, A H3N2 92%, B 33%	6 months; A H1N1 45%, A H3N2 95%, B 32%

DT=diphtheria and tetanus vaccine. EIA=enzyme immunoassay. IU=international units. IE=internationale einheit. DTaP=diphtheria, tetanus, and acellular pertussis vaccine. Td=tetanus and diphtheria vaccine. TT=tetanus toxoid. LPA=lymphoproliferative assay. SI=stimulation indices. EU=ELISA units. HAI=haemagglutination inhibition assay. TIV=inactivated trivalent influenza vaccine. OPA=opsonophagocytic activity. ISR=immune status ratio. ELFA=enzyme-linked fluorescent assay. AU=arbitrary units. PPV=pneumococcal polysaccharide vaccine. MMR=measles, mumps, and rubella vaccine. FAMA=fluorescent antibody membrane assay. LAIV=live attenuated influenza vaccine. *Indicator for whether this was a new vaccine given to children for the first time while on HAART or revaccination for a vaccine given before started on HAART. †Early represents children who were started on HAART within the first year of life. Late control represents children who were started on HAART after age 1 year in whom viral suppression was achieved. Late failure represents children who were started on HAART after age 1 year in whom viral suppression was not achieved. ‡Calculated using specific IgG levels and incidence of invasive *Streptococcus pneumoniae* isolated in the USA and summed over all serotypes. §Values estimated from box plots.

Table 3: Studies reporting immune response to vaccination while receiving HAART

study also examined changes in influenza-specific antibodies and lymphocytes within the first 6 months after vaccination.[43] Increases were reported for IgG3 antibodies, CD8 interferon-γ-secreting T lymphocytes, and CD4 interleukin-2-secreting T lymphocytes 1 month after vaccination. There was a subsequent decline to almost baseline levels 6 months after vaccination. The increase at 1 month was only statistically significantly different from baseline for CD8 interferon-γ-secreting T lymphocytes. For pneumococcal vaccine, immune responses remained stable by serotype (81% to 75% from 8 weeks to 80 weeks for serotype 1, 92% to 92% for 6B, 92% to 88% for 14, 96% to 95% for 19F, and 76% to 74% for 24F).[32] For HAV, the proportion of children with an immune response declined from 72% at 4 weeks to 66% at 52 weeks after vaccination,[28] and from 97% at 8 weeks to 90% at 18 months in two studies from the USA.[38]

Lymphoproliferative responses were assessed in several studies (table 3). The proportion of children responding within 3 months of vaccination was 47–86% for tetanus toxoid,[22,23,26,28] and 17% for diphtheria toxoid.[23] For tetanus toxoid, Rigaud and colleagues[28] reported a decrease in lymphoproliferative responses 52 weeks after vaccination (73% at 4 weeks to 61% at 52 weeks). For HAV, the proportion of children responding at 4 weeks (12%) and 52 weeks (13%) was similar.[28]

Predictors of response to vaccination while receiving HAART were investigated in several studies. For tetanus toxoid, lymphoproliferative responses and antibody concentrations were higher for children who had undetectable viral load before study vaccination than for children who did not, although the proportions who were positive were not statistically different between the two groups.[26] Additionally, children with higher percentages of naive T cells (CD4+/CD62L+/CD45RA+) after study vaccination had better responses, although age was not associated with the response.[24] For pertussis, greater antibody concentration, greater proportions of CD4 T cells, and lower HIV viral load 24 weeks before study vaccination were associated with higher antibody concentrations after revaccination, whereas nadir proportions of CD4 T cells (ever or before HAART) were not associated.[25] For pneumoccocal vaccine, older age,[29] higher antibody concentration,[32] greater proportions of CD4 T cells[29,32] and lower HIV-1 viral load[32] at study vaccination, and longer duration of HAART,[32] were associated with better response in some studies, but not in others.[29,30] Other characteristics, such as race, sex, and clinical status before starting HAART or at study vaccination were not associated with response.[29,30,32] For HBV vaccine, lower HIV-1 viral load at the first dose of study vaccination[35,37] was associated with better response, although duration of HAART and viral load before HAART were not.[35,36] Inconsistent results were found for antibody concentration at vaccination, age, and immune status at revaccination.[35,37] For influenza, higher antibody concentrations at study vaccination were associated with

better response,[54] although age, sex, and immunological status were not associated.[43,54] Lower HIV-1 viral load at study vaccination was associated with better response in one study[54] but not another.[42] For HAV, greater proportions of CD4[39,40] and CD8 T cells,[39] lower HIV-1 viral load,[38–40] greater proportions of B cells (CD19) at study vaccination (first dose),[39] detectable cell-mediated immunity[39] after vaccination, and proportion of CD4 T cells at second dose,[38] were associated with better response. Age, sex, and race were not associated with response in any study.[38–40] The proportion of naive and memory T cells were not associated with response to HAV vaccination.[39]

Two studies were specifically designed to assess the effects of duration of HAART and timing of HAART initiation in relation to vaccine responses. In the study by Rigaud and colleagues,[28] children starting HAART were randomised to receive vaccines at 8 weeks and 32 weeks after study enrolment. Children received either tetanus toxoid and then HAV or HAV and then tetanus toxoid to assess the effect of the level of immune reconstitution on vaccine responses. For tetanus toxoid in children who previously received vaccinations before starting HAART, lymphoproliferative responses, antibody concentrations, and serological response did not differ between the two groups (100% vs 89% 4 weeks after completing vaccine series; 100% vs 81% after 1 year). For HAV in children who received their first dose after starting HAART, children who received HAV vaccine at 32 weeks had substantially greater antibody concentrations than children who received the vaccine at 8 weeks. The proportion of responders was also greater (88% vs 60% 4 weeks after completing vaccine series; 86% vs 50% after 1 year), although not statistically different.

In the study by Pensieroso and co-workers,[53] immunity to childhood vaccines was assessed among children who started HAART at different ages (either early, within the first year of life, or late, after the first year of life) to establish the effect of the timing of HAART on vaccine responses. The investigators did not report whether children in the early group were given their primary vaccine series before or after starting HAART, therefore, whether the study assessed the timing of HAART in relation to age or vaccination is unclear. Antibodies to tetanus toxoid were higher in the early treatment group than in the late treatment group, with higher responses in the late treatment group that achieved HIV-1 suppression than in the late treatment group that did not (figure). A similar trend was noted for antibodies to pneumococcus, although these results were not statistically significant.

When compared with healthy, HIV-uninfected controls, children infected with HIV taking HAART tended to have lower antibody concentrations or lower protective immunity for pneumococcal antigens[29] and influenza (figure).[42,43] For influenza, children infected with HIV had lower concentrations of influenza virus-specific IgG3, but not IgG1, antibodies, CD8 interferon-γ-secreting

T lymphocytes and CD4 interleukin-2-secreting T lymphocytes than did healthy controls.[43] In the study by Pensieroso and colleagues,[53] children in the early treatment group had similar antibody concentrations to tetanus toxoid and pneumococcus as children in the control group, but those in the late treatment group tended to have lower antibody concentrations than did children in the control group. Children infected with HIV not receiving HAART had lower antibody concentrations after vaccination against HBV than did children receiving HAART;[36] however, this was not true for tetanus toxoid (figure).[53] Noted differences between children receiving and not receiving HAART likely depend on the immunological and virological status of children not receiving HAART at the time of vaccination.

Vaccine safety was reported in several studies. No serious, potentially life-threatening adverse events were reported for tetanus toxoid,[24,28,52] pertussis,[25] HAV,[28,38] HBV,[35–37] influenza,[42,43,54] or pneumococcal vaccine.[32] Mild adverse events were reported for HBV[35,36] and influenza vaccination, including pain or swelling at the injection site and fever. These events were reported by 16% of children infected with HIV, compared with 14% of uninfected children, receiving influenza vaccination in one study.[43] In another study,[54] 33% of children infected with HIV that received influenza vaccination reported grade 1 events (mild, no intervention required), 24% reported grade 2 (moderate, minimal intervention required), and 2% reported grade 3 (severe, medical care required). Grade 3 events included fever and injection site swelling. For pneumococcal vaccine, 5% of participants reported at least one vaccine-related grade 3 event, including localised or generalised erythema, induration, and pain.[32] An additional 1% of participants reported possible vaccine-related events, including fever, neutropenia, and pharyngitis. No studies reported adverse changes in CD4-T-cell counts or proportions, or in plasma HIV-1 viral loads, after vaccination.[24–26,28,32,35,41,42,54]

Live viral vaccines

For replicating vaccines, studies were available for MMR, varicella, and live attenuated influenza vaccines (table 3). For most vaccines, with the exception of varicella, children were revaccinated with vaccines first received before starting HAART. Within the first 3 months after vaccination, the proportion of children responding to vaccination, as defined by each study, was 64–90% for measles,[45,47,52,55] 61% for mumps,[47] 80–100% for rubella,[46,47] 71% for varicella,[49] and 33–92% by strain for influenza.[50,54] In studies of long-term responses to vaccination (>3 months), the proportion of children with an immune response was 39–82% for measles,[48,53,55] 89% for mumps,[48] 80% for rubella,[48] 65% for varicella,[49] and 32–95% by strain for influenza.[54] Several studies assessed both short-term and long-term immunity and generally found that immunity decreased with time. For measles, one study in the USA[55] reported that the proportion of children with

detectable antibodies decreased from 83% at 4 weeks to 73% at 52 weeks after revaccination. For varicella, the proportion of children who were seropositive decreased from 71% at 8 weeks after vaccination to 65% at 52 weeks, 47% and 104 weeks, and 38% at 156 weeks.[49] For influenza, the proportion of children with protective immunity remained steady through 24 weeks after vaccination.[54]

Lymphoproliferative responses were only reported from one study assessing varicella vaccine in the USA.[49] The proportion of children with positive lymphoproliferative responses was 85% at 8 weeks after vaccination, 92% at 52 weeks, 85% at 104 weeks, and 33% at 156 weeks.

Risk factors for response to vaccination were inconsistent. Several studies found no association with the proportion of CD4 T cells and viral load at the start of HAART or revaccination against measles with MMR vaccine,[45,47] although one study reported these associations for rubella at the time of revaccination.[46] Age, sex, and duration of HAART were not associated with response to MMR vaccine.[47] In the study by Pensieroso and colleagues,[53] children who were started on HAART early had greater measles antibody concentrations and were more likely to have protective immunity compared with those who were started on HAART after the first year of life. For varicella, immune response after each dose was associated with HIV-1 viral load but not proportion of CD4 T cells at first dose.[49] Additionally, immune responses to subsequent doses were more likely to be positive if the prior response was positive.

When compared with a control group of people not infected with HIV, children infected with HIV on HAART had lower antibody concentrations for measles and rubella and were less likely to have protective immunity (figure).[46,53] However, these findings were limited to children who were started on HAART after the first year of life in the study by Pensieroso and colleagues,[53] and to children with evidence of moderate or severe immunosuppression in the study by Lima and co-workers.[46] For live intranasal influenza vaccine, children on HAART had similar responses to vaccination compared with uninfected people in the control group.[50] When compared with children infected with HIV not on HAART, a higher proportion of infected children on HAART developed protective immunity to varicella[49] and measles,[45,53] although in the study by Pensieroso and colleagues,[53] this was true only for children who were started on HAART in the first year of life.

Vaccine safety was assessed for measles, varicella, and influenza. For measles vaccine, no serious adverse events were reported;[47,52] mild events included pain at the injection site (23 patients; 45%).[47] For varicella vaccine, one (6%) patient reported reactions at the injection site (none were grade three) and two (12%) reported systemic reactions (none were grade three), including fever, otitis media or sinusitis, rash, and "viral syndrome", after the first dose of vaccine. Two (12%) children had local reactions after the second dose of vaccine (one [6%] grade three) and five (29%) had systemic reactions (one [6%]

grade three).[49] For the live intranasal influenza vaccine, 60 (49%) patients reported grade one events, 23 (19%) grade two, and three (2%) grade three. Grade three events included malaise, finger pain, and leg boils, only one of which was thought to be vaccine related (not specified).[54] A second influenza vaccine trial[50] reported that 14 (61%) children infected with HIV experienced reactogenicity events after the first dose of the vaccine and five (33%) after the second dose, including fever, cough, headache, and nausea or vomiting. Five (22%) children had possible vaccine-related adverse events after the first dose and two (13%) after the second dose, including otitis media, upper respiratory illness, sinusitis, wheezing, and coughing. Rates of events did not differ between infected and uninfected children.[50] No studies reported any adverse changes in CD4-T-cell counts or proportions, or in plasma HIV-1 viral loads, after vaccination.[47,49,50,54]

Discussion

The proportion of children with immunity after being started on HAART is low for most vaccines studied, but no characteristic consistently predicted immunity after starting HAART. In general, children infected with HIV on HAART developed immune responses within several months of vaccination, with no differences in the level of primary or secondary responses to new or previously received vaccines. However, immunity waned in some children. In some studies, children on HAART who had a higher CD4-T-cell count and lower plasma HIV-1 viral load at vaccination were more likely to develop immunity.

HAART is unlikely to restore memory T cells for vaccine antigens to which children were exposed before treatment, but should restore the ability of the immune system to respond to new antigens. Few studies measured immunity before and after the start of HAART. In studies that measured immune responses only after HAART, it was not possible to establish whether the noted low levels of immunity were due to a lack of primary response to vaccination before HAART or the inability of HAART to restore waning immunity. From the few studies that measured immune responses both before and after HAART, some children did regain immunity to vaccine-preventable diseases after being started on HAART. However, many children lost measurable antibody responses to vaccine antigens after being started on HAART, potentially as a result of the shorter lifespan of plasma cells and persistent B-cell abnormalities in children infected with HIV.[56] Consequently, levels of immunity to vaccine-preventable diseases in this population remained low, suggesting that the majority of children on HAART would benefit from revaccination. Waning immunity after revaccination and vaccination with new vaccines was greater and more rapid than in children not infected with HIV, who typically maintain high antibody concentrations years after vaccination.[57] Waning immunity among children

infected with HIV on HAART can be explained by persistent B-cell abnormalities in children[22,58] and adults[56,58,59] despite increases in the number and function of CD4 T cells. Most notable are the loss of memory B cells and a decrease in memory B cell function in treatment-naive patients that are not fully reversed after starting HAART. These losses are associated with defects in antigen-specific memory-B-cell responses to both T-cell-dependent and T-cell-independent antigens,[56,58] and might affect long-term responses to vaccination in children on HAART.

The best timing of vaccination after starting HAART is not known, both for revaccination and primary vaccination with new vaccines, and few studies address this important question. Most studies found that higher CD4-T-cell counts and lower HIV-1 viral loads were crudely or independently associated with higher levels of immunity after vaccination on HAART, suggesting sufficient time should be allowed to restore immune function and suppress viral replication. Only one published study[28] was specifically designed to examine this issue. Children who received HAV vaccine for the first time more than 6 months after being started on

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Panel: Study findings and implications for revaccination of children infected with HIV on HAART

Findings

- Children on HAART generally have low immunity to childhood vaccines received before starting HAART
- Children on HAART generally mount good antibody and lymphoproliferative responses to revaccination during therapy
- Children vaccinated while on HAART can lose protective immunity over time
- Timing of HAART, in relation to age, degree of immunosuppression, and primary vaccination status can influence response to vaccination
- Gaps in knowledge:
  - The best timing of revaccination after starting HAART
  - The effect of age at the start of HAART on response to revaccination
  - Responses to primary vaccination after starting HAART
  - Necessity for and timing of repeat doses after revaccination while on HAART
  - Relation between antibody concentrations and protective immunity

Implications

- HAART does not restore immunity to prior vaccination
  - Children on HAART would probably benefit from revaccination against childhood diseases
- HAART might not ensure long-lasting immunity
  - Repeat or higher doses might be needed for some children
- Children who start HAART in infancy might retain functional immunity and have better responses to vaccination
  - Continued efforts are needed to identify and treat HIV-infected children at younger ages and earlier stages of disease
- Initial vaccination or revaccination after viral suppression and immune reconstitution might improve immune responses to vaccination
  - Children with poor treatment responses might remain susceptible to vaccine-preventable diseases and might need to be monitored for adequate levels of protective immunity and possibly revaccinated when treatment responses improve

Search strategy and selection criteria

We searched PubMed for articles published in English before April 1, 2010, by use of the terms "HIV", "antiretroviral therapy", and "vaccine" (n=835), and also "HIV", "therapy", and "vaccine" in combination with "tetanus" (n=60), "pertussis" (n=11), "diphtheria" (n=16), "mumps" (n=21), "hepatitis" (n=229), "influenza" (n=89), "pneumococcal" (n=93), "measles" (n=35), "Haemophilus" (n=19), "varicella" (n=25), and "yellow fever" (n=4). Additionally, we reviewed citations within relevant studies. Studies were included if they involved children (mean or median age <16 years) in whom most (>95%) were receiving HAART or if the results were stratified by receipt of HAART; and they either described cellular or humoral immunity to at least one vaccine-preventable disease after the start of HAART but before revaccination, or they described cellular or humoral responses to vaccination after the start of HAART. Studies were excluded if pooled antigens were used or the type of antiretroviral therapy could not be established.

HAART had higher immunity than did those who received HAART for only 2 months.[28] However, duration of HAART was not associated with improved responses to tetanus toxoid, a vaccine that children first received before being started on HAART, suggesting a lower level of immune reconstitution might be sufficient to induce a memory response. Prospective studies of children infected with HIV are needed to establish the best timing of revaccination and whether this response differs by vaccine.

Age of the patient when started on HAART, particularly in relation to the timing of vaccination, might be important in enhancing vaccine responses. In one study,[53] children who were started on HAART in infancy (<12 months) had greater protective immunity than did children who were started on HAART later in childhood, and had similar levels of immunity with uninfected children of the same age. Early administration of HAART preserved the memory B-cell compartment. The restoration of immune function in infants on HAART might be similar to the immunological benefits noted among adults treated during acute infection.[60–63] Many children in the early treatment group probably received some of their primary vaccinations after being started on HAART. For all vaccines studied, immune reconstitution seems to have allowed this group to both preserve immune responses to previously received vaccines and successfully mount and maintain an immune response to new vaccines. These findings support recommendations for early administration of HAART among infants, which reduces HIV-related morbidity and mortality.[64]

Several issues limit study comparability and the inferences drawn from their review. First, although many studies were identified that assessed immunity or vaccine responses among children infected with HIV on HAART, few studies were identified for each vaccine, which limited comparisons. Second, great heterogeneity existed across studies in the type of study design, eligibility criteria on the basis of immunological and virological status, characteristics of the study population (including age, disease stage, and duration of HAART), assays used to measure immune responses, definition of immunity, and the presence of a comparison group. These factors also limited the comparability of study results. Third, vaccine-induced immunity could not be distinguished from immunity derived from natural infection. This problem is particularly relevant for studies with a long interval between the start of HAART, vaccination, and measurement of antibody levels, and obviously depends on the incidence of wild-type infection in the study population. Last, all identified studies used surrogate markers of protective immunity, specifically antibody concentrations and lympho-proliferative responses. How well these markers correlate with protective immunity in children infected with HIV on HAART is not known and data on vaccine efficacy in this population are lacking.

Despite these differences, the broad findings were consistent (panel). Most children treated with HAART remained susceptible to vaccine-preventable diseases, and in some children, immune responses to vaccines received before treatment were lost after the start of HAART. Most children receiving HAART, however, responded to vaccination but immune reconstitution was not sufficient to ensure long-term immunity for some children. Many children in low-resource settings start taking HAART at older ages, after having received their primary vaccine series.[16] As treatment programmes scale-up and more children receive HAART and live into adolescence and adulthood, a larger proportion of these children might be susceptible to vaccine-preventable childhood diseases. Levels of protective immunity in these children will need to be monitored, and some children might need additional doses of vaccines to maintain protective immunity. Vaccination policies and strategies for children infected with HIV on HAART should be developed in regions of high HIV prevalence to ensure adequate levels of population immunity. Starting HAART in infancy, before receipt of routine childhood vaccines, might preserve immunity to vaccine-preventable diseases. Consequently, efforts should continue to identify infants and children infected with HIV and start treatment as early as possible. Further studies are needed on the nature and longevity of immune responses among infants on HAART, and vaccination policies might need to be reviewed and revised as more children start treatment in infancy.

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