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Immunogenicity following the first and second doses of 7-valent pneumococcal conjugate vaccine in HIV-infected and -uninfected infants☆,,☆☆

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Abstract

Background—The immunogenicity of pneumococcal conjugate vaccine (PCV) has not been evaluated in HIV-infected infants following the first and second PCV-doses. We studied antibody kinetics of serotypes included in 7-valent PCV in HIV-infected and HIV-uninfected infants prior to and following each of three PCV-doses.

Methods—HIV-uninfected infants born to HIV-uninfected (HUU) and HIV-infected mothers (HEU); and perinatal HIV-infected children with CD^{4+} < 25% randomized to initiate antiretroviral treatment (ART) when clinically and/or immunologically indicated (ART−) or immediately (ART +) were enrolled. Vaccination occurred at approximately 7.4, 11.5 and 15.5 weeks of age.

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Authors contribution: SAM, AV, MC and PVA contributed to the conceptualisation and design of the study. AI and SAM were involved in data analysis. RP was involved in data management. PS, NvN and PVA were responsible for the laboratory assays. SAM, AV, ED and MC were involved in participant enrolment and follow-up. PJP was involved in the conduct of the study and contributed to the manuscript write-up. The first draft was written by SAM. All the authors subsequently critically reviewed the manuscript and approved the final version.

Appendix A. Supplementary data Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2012.11.076.

Serotype-specific antibody was measured by ELISA following each PCV-dose and opsonophagocytic activity (OPA) to three serotypes following the second and third doses.

Results—Pre-vaccination, antibody geometric mean concentrations (GMCs) were higher in HUU compared to HIV-exposed groups for most serotypes. GMCs and proportion of infants with antibody ≥0.35 μg/ml were similar in HUU compared to other groups following the second PCV-dose. In all groups, GMCs were greater following the third compared to post-second dose; and a higher proportion within each group had antibody ≥0.35 μg/ml to 6B and 23F. OPA GMTs increased after the third compared to post-second dose for studied-serotypes; as did the proportion with OPA ≥8 to 23F.

Conclusion—A two-dose primary-series of PCV probably confers similar protection against invasive pneumococcal disease in HIV-infected compared to HUU children. The inferior response to serotypes 6B and 23F, and lower GMCs and OPA GMTs, following two compared to after three PCV-doses may have implications in the prevention of pneumococcal disease in high-burden countries.

Keywords

Streptococcus pneumoniae; Pneumococcal conjugate vaccine; Dosing schedules; HIV; Opsonophagocytic assay

1. Background

Pneumococcal conjugate vaccines (PCV) are licensed as a three-dose primary-series before seven months of age with a booster in the second year of life. Many infant immunization programs have, however, implemented alternate dosing schedules, including a two-dose primary-series with a booster dose later [1]. This is aimed at reducing the overall costs of PCV immunization and number of injectable vaccines during childhood. Recent WHO recommendations on infant PCV immunization recommend a three-dose primary-series or two doses followed by a booster dose at least 6 months later [1]. This decision was informed in-part by meta-analyses, without any study identified in HIV-infected children, of the immunogenicity and effectiveness of different PCV dosing schedules [2,3].

The potential effect of fewer doses of PCV in HIV-infected children, who contribute toward a high burden of invasive pneumococcal disease (IPD) in sub-Saharan African countries [4], requires study. A three-dose primary-series of 9-valent PCV without a booster dose was less efficacious against vaccine-serotype IPD in anti-retroviral treatment (ART) naïve HIV-infected (65%) compared to HIV-uninfected children (85%) after 2.3 years of follow-up [5]. Furthermore, there was waning of protection against IPD five years post-vaccination in the HIV-infected children [6]. The lower efficacy of PCV in HIV-infected children was corroborated by poorer qualitative antibody responses, measured by opsonophagocytic activity assay (OPA), following the three-dose primary-series compared to HIV-uninfected infants [7]. Also, greater decay of antibody was observed in HIV-infected compared to HIV-uninfected children five years post-vaccination [6]. Consequently, a three-dose primaryseries coupled with a booster dose of PCV may be required in ART− naïve HIV-infected children.

There have, however, been recent changes in the management of HIV-infected infants, including early initiation of ART irrespective of their immunological status [8]. Similar quantitative and OPA responses following three doses of PCV during infancy were observed in HIV-infected infants initiated on ART immediately at 6–12 weeks of age as HIV-uninfected children [9]. This analysis of secondary-study objectives expand on our previous report on the quantitative and OPA responses following the third infant PCV-dose in HIV-

infected and HIV-exposed-uninfected children; and infants born to HIV-uninfected mothers (HUU) [9].

The secondary-objectives analyzed in this report include: (i) comparison of pre-vaccination PCV-serotype antibody concentrations; (ii) comparison of antibody responses following the first and second-PCV-doses between HIV-infected and HEU children compared to HUU infants; (iii) comparison of the antibody responses and OPA responses after the second compared to post-third PCV-dose (which we previously reported [9]) within each group and relative to HUU infants.

2. Methods

2.1. Study cohort

Detailed information of the study-cohort enrolled between April 2005 and June 2006 has been described. [9] Briefly, four groups of children aged 6 to 12 weeks were enrolled to address a co-primary study objective of quantitative antibody responses following the three-dose primary-series at 6, 10 and 14 weeks of 7-valent PCV (i.e. Prevnar®; Wyeth Vaccines, NJ, USA). Study-groups included HIV-infected infants, co-enrolled from the Children with HIV Early Antiretroviral (CHER) Study in South Africa [10], with CD^{4+} T-lymphocyte ≥25% randomized to either initiate ART immediately (ART+); or deferred (ART−) until clinically or immunologically indicated [10]. Also, a convenience sample of HIV-infected children with CD^{4+} < 25%, who were immediately initiated on ART, were enrolled (Group-5). The first-line ART regimen used in CHER included zidovudine, lamivudine and lopinavir/ritonavir. Methodology for HIV PCR, HIV ELISA and CD^{4+} count testing has been published [10].

In parallel to enrolment of HIV-infected children from CHER, two cohorts of HIV-uninfected children were also enrolled. This included infants born to HIV-infected mothers who were HIV PCR (Roche Amplicor Version 1.5 RNA PCR) negative at baseline and one month after the third PCV-dose (i.e. HEU); and children born to HIV-uninfected mothers who had a non-reactive HIV-ELISA at study-enrolment (HUU).

2.2. Study procedures

Venous blood samples were collected prior to the first PCV-dose, immediately prior to each of three subsequent PCV-doses and 3–6 weeks after the third dose and processed at Respiratory and Meningeal Pathogens Research Unit (RMPRU), Johannesburg, South Africa. Vaccine-serotype specific capsular IgG antibodies were measured using a standardized enzyme immunoassay (EIA) as described [9].

Antibody functionality post-second and third PCV-doses were determined by OPA for serotypes 9V, 19F and 23F as described. [9]. The coefficient of variation for the control sera, from a vaccinated-volunteer, which was included on each plate were 9.9%, 9.7% and 9.3% for serotypes 9V, 19F and 23F respectively post-second dose.

2.3. Statistical analysis

Data were analyzed using SAS® 9.1 (SAS Institute Inc., Cary, NC, USA). The geometric mean concentrations (GMC) or titers (GMT) and 95% confidence intervals (95% CI) of serotype-specific antibody concentrations and OPA titers were calculated following $\log_{10}$ data transformation. Comparisons of GMC or GMT were performed using analysis of covariance (ANCOVA) on $\log_{10}$ transformed data with study center, gender, race and baseline antibody concentration (for post-vaccination measures) as covariates. Samples with values below the assay detection limit were assigned half the detection limit when

calculating GMC or GMTs. Logistic regression with study-center, gender and race as covariates were applied for comparisons of proportion of children in groups with serum antibody thresholds of ≥0.35 μg/ml; i.e. a putative measure of community-immunity against vaccine-serotype IPD [1].

If the maximum observed killing of pneumococci by HL-60 cells on OPA was less than 50%, at the lowest dilution, the serum was assigned an arbitrary titer of 4 [9]. Detectable killing activity on OPA was defined as a titer of ≥8. An α value of ≤0.05 was considered significant.

To minimize confounders between groups, only children in whom all previous study procedures were undertaken within protocol specified window-periods up to the analyzed time-point were evaluated. No statistical comparisons were undertaken for Group-5 because of its small sample size.

2.4. Ethics considerations

This study was approved by the Human Subjects Research Committees of the University of the Witwatersrand, Stellenbosch University, the Medicine Control Council of South Africa and Clinical Science Review Committee of the Division of AIDS. Signed informed consent was obtained from the parents of the children for participation in this study. The study was registered at ClinicalTrials.gov NCT00099658.

3. Results

Overall, 579 children were enrolled between the five groups. Further analysis was limited to 565 children in whom the immunogenicity evaluation following the first PCV-dose was undertaken within the protocol specified window-period. The mean age at vaccination and timing of antibody measures are detailed in Table 1. The median HIV-1 viral load was ≥750,000 copies/ml in HIV-infected children; and median CD4% were 35.5%, 36.6% and 21.8% among ART+, ART− and Group-5, respectively.

3.1. Geometric mean antibody concentrations

Pre-vaccination, HUU children had higher GMCs to all serotypes compared to HEU infants ($p \leq 0.006$ for all observations), as well for at least three serotypes (either 9V, 18C, 19F or 23F) compared to ART+ and ART− children; Table 2. Baseline GMCs were also higher for all serotypes, except 18C ($p = 0.24$), in HIV-infected children overall (i.e. combined ART+, ART− and Group-5) compared to HEU children ($p \leq 0.001$ for all comparison; composite overall GMC data of HIV-infected children not shown).

Compared to HUU infants, GMCs following the first PCV-dose were lower in HEU and ART+ children for four serotypes, whilst not being significantly different for any serotype in ART− children; Table 3. Following the second PCV-dose, GMCs were generally similar for at least six serotypes in HUU compared to each of the other groups; Table 3. GMCs were generally similar between ART+ and ART− children following each of the first two PCV-doses ($p > 0.087$ for all comparisons), except 9V was higher in ART+ ($p = 0.046$) following the second PCV-dose. Between-group comparisons of post-third PCV-dose have been reported [9].

Significant increase in GMCs were observed in HUU, HEU and ART+ children for all serotypes comparing post-second to post-third dose within each group. Similarly, increases were also observed for serotypes 6B, 9V, 14, 23F in ART− children; and a likewise trend for the other serotypes; Table 3.

3.2. Comparison of proportion with serotype-specific antibody ≥ 0.35 μg/ml

The proportion of children with serotype-specific anti-capsular antibody ≥0.35 μg/ml pre-vaccination ranged between 20 and 77% in HUU children, which was significantly higher for all serotypes compared to HEU children ($p < 0.005$), and for at least three serotypes (including 18C, 19F and 23F) in ART+ and ART− children; Table 2. Relative to HIV-infected children combined, a lower proportion of HEU had antibody ≥0.35 ug/ml to serotypes 4, 6B, 14, 19F and 23 pre-vaccination ($p \leq 0.029$ for these serotypes).

Following the first PCV-dose, a higher proportion of HUU children had antibody ≥0.35 μg/ml (range 26–82%) for most serotypes compared to HEU (6B, 9V, 14, 19F and 23F) and ART+ (6B, 9V, 19F and 23F) children; Table 4. The proportion of children with antibody ≥ 0.35 μg/ml following the second PCV-dose was, however, similar between HUU and other groups; except being lower for serotype-4 in HEU and higher for 6B but lower for 9V in ART− children. Antibody concentrations ≥0.35 μg/ml were consistently lowest against serotypes 6B (range 35–60%) and 23F (range 79–87%) in all groups following the second PCV-dose; Table 4. Relative to all HIV-infected children, a similar proportion of HEU had antibody ≥0.35 μg/ml to most serotypes following the first and second PCV-doses; except being lower for 6B ($p = 0.046$) and 14 ($p = 0.013$) after the first PCV-dose; and for 6B ($p = 0.003$) after the second PCV-dose.

Increase in the proportion of subjects within each group with antibody ≥0.35 μg/ml after the second compared to after the third PCV-dose was consistently observed for 6B in all groups, 23F in HUU, ART− and ART+ infants; and serotype 14 in HEU and ART+ children. The difference in proportion with antibody ≥0.35 μg/ml following the third compared to post-second PCV-dose was greatest for 6B in all groups; $p < 0.005$ for all comparisons (Table 4). We also analyzed the proportion of infants with anti-6B antibody ≥0.20 μg/ml, i.e. an alternate threshold proposed as more accurately predictive of protection against IPD from this serotype [11]. Following the second and third PCV-doses (Supplementary Table 2), significant increases in proportion with antibody ≥0.20 μg/ml were observed, including from 61% to 89%, 59% to 96%, 66% to 95% and 75% to 95% in HUU, HEU, ART+, ART− children, respectively ($p \leq 0.004$ for all observations).

3.3. Opsonophagocytic activity assay responses following the second and third dose of PCV

There was absence of consistency in the pattern of OPA responses between groups following the second PCV-dose. Whilst OPA GMTs were similar in HUU compared to other groups for 19F, GMTs were higher in HUU compared to ART− for 9V and lower in HUU for 23F compared to ART−, ART+ and HEU children; Table 5. Significant increases in OPA GMTs were observed between the second compared to after the third PCV-dose in all study-groups, except for 9V in HEU; Table 5.

The proportion of children with OPA ≥8 after the second PCV-dose were >88%, 86% and 67.5% for serotypes 9V, 19F and 23F, respectively; and did not differ between HUU and other groups; Table 5. The proportion of children with OPA ≥8 after the third compared to the second PCV-dose tended to be higher in each group for all serotypes, but only significantly so for 23F; Table 5.

4. Discussion

To our knowledge, this is the first study to report on immune responses following the first and second PCV-doses in HIV-infected and HEU infants. Relative to HUU, the proportion of children with antibody ≥0.35 μg/ml following the second PCV-dose was similar for all serotypes in HEU and ART+ children; and for most serotypes in ART− children. This

suggests that a two-dose primary-series schedule in HIV-infected infants, regardless of ART status, and in HEU children may afford similar protection against vaccine-serotype IPD compared to HUU children. The similarity in antibody responses following the second compared to after the third PCV-dose was further corroborated by the similar proportion of children with OPA ≥8 for serotypes 9V and 19F in all groups (except 9V in ART+) following each dose.

Of note, however, was the consistently higher proportion of children within each group who had antibody ≥0.35 μg/ml to serotypes 6B and 23F, as well as higher proportion with OPA ≥8 to serotype-23F, following three compared to after two PCV-doses. Although OPA responses to 6B were not measured in our study, the superiority of three compared to two PCV-doses for protection against 6B was also evident when using a lower threshold of ≥0.20 μg/ml, which correlates well with proportion of children with OPA ≥8 for 6B [11]. The lower immunogenicity to 6B and 23F observed in our study is consistent with the findings of meta-analyses, which evaluated the immunogenicity of two and three PCV-doses [2,3]. The inferior immune response to serotypes 6B and 23F, following the second compared to after the third PCV-dose, is clinically concerning as they are the second and fourth most common serotypes associated with childhood IPD globally, and collectively responsible for approximately 20% of childhood-IPD [12]. Although serotypes 6B and 23F are ranked as being the fourth (7% of total) and sixth (5% of total) most common IPD causing serotypes in low-income countries, respectively, this needs to be interpreted in the context of the high burden of pneumococcal disease in such countries [12].

In addition to immunogenicity, other factors which warrant consideration when deciding between different dosing schedules include the “immunity-gap” which may prevail, particularly when the second PCV-dose is given two-months after the first dose, as is recommended, so as to enhance antibody responses compared to when doses are spaced one-month apart [11]. This potential immunity-gap is pertinent since approximately 15% of IPD in South Africa occurs in children <3.5 months of age [13]. Based on the immune responses following the first dose, less than 50% of children in any group would have been protected against the majority of vaccine-serotypes until approximately 3 months of age, if the second dose is only scheduled at 14-weeks of age. Furthermore, this immunity-gap would be greater in ART+ and HEU compared to HUU infants for at least four serotypes. Possibilities of addressing this immunity-gap include providing the first PCV-dose at birth, [14] or providing passive protection during early-infancy through pneumococcal-vaccination of pregnant-women [15]. This immunity-gap during early infancy may become less important following widespread PCV-immunization of young children, because of the interruption of vaccine-serotype transmission in the community following immunization of young-children. This indirect-effect has been associated with reduction of vaccine-serotype IPD, including in infants too young to have been vaccinated [16].

The potential effectiveness of a reduced dose primary-series against non-bacteremic pneumonia, which accounts for the majority of severe pneumococcal illness and >90% of pneumococcal associated mortality, should also be considered when deciding on dosing schedules. The anti-capsular antibody threshold of ≥0.35 μg/ml or OPA ≥8 is only putative-measures of community-protection against IPD, whereas higher antibody concentrations may be required to protect against pneumonia. In this regard, GMCs and OPA GMTs were lower for almost each serotype in all groups following the second compared to after the third PCV-dose. Lower protection against hospitalized and out-patient pneumonia has been reported for infants receiving two compared to three PCV-doses [17]. A two-dose primary PCV schedule is, however, likely to provide some protection against mucosal infections as indicated by the reduced risk of nasopharyngeal acquisition of vaccine-serotypes at 12 months of age in children receiving two doses compared to no PCV-vaccination [18].

Reduction in pneumonia has also been reported in ecological studies from countries using two doses during infancy and a later booster dose, [19–21] including prior to the booster dose [19].

The lower GMCs observed pre-vaccination in all Groups born to HIV-infected mothers compared to HUU children, may be due to lower anti-capsular antibody in HIV-infected mothers and possible impairment of transplacental antibody transfer to HIV-exposed children. However, the reason for the lower GMCs in HEU compared to HIV-infected children prior to PCV-vaccination is unknown. Possible reasons may include: (i) unregulated increase in non-specific antibody production in HIV-infected children prior to ART− initiation related to uncontrolled HIV-viral replication decreasing regulatory T-lymphocytes; and/or (ii) higher transplacental transfer of antibody due to impaired placental function in newborns who acquire HIV from their mothers in utero [22]. The lower antibody concentrations to pneumococcus may contribute to the increase in early-infant morbidity and mortality observed in HEU compared to HUU children [23].

Limitations of our study included only enrolling a convenience sample in Group-5, which was inadequate for statistical comparisons to other groups. The quantitative and qualitative antibody responses in Group-5 were, however, similar to ART+ children following the second and third PCV-doses (Tables 2 and 3 and Supplementary table* 1). Furthermore, we only evaluated OPA responses to three serotypes, which inadvertently excluded serotype 6B for which poor antibody responses were observed following two PCV-doses. Except for 6B, however, OPA titers ≥8 generally correlate closely with antibody concentrations ≥0.35 ug/ml for the other seven-valent PCV-serotypes [2]. Also, in-utero HIV infection status, although implied, was not confirmed in our study. Additionally, this study did not randomize children to different dosing schedules, but opportunistically compared immune responses after the second and third PCV-doses. Nevertheless, because the vaccines were only spaced one-month apart in our study, it probably provides a conservative measure of the immune response after the second dose, compared to if the first two doses were spaced at least two months apart, [11] as is currently practiced in South Africa.

In conclusion, a primary PCV dosing-schedule comprising two doses is likely as efficacious as three doses against IPD in HIV-infected compared to HUU infants. The inferior immunogenicity of a two-dose compared to three-dose primary-series schedule against two important IPD causing serotypes (6B and 23F) in children is, however, a potential drawback of two-dose schedule in countries with a burden of IPD during early infancy. Also, a two-dose primary-series may be associated with a further immunity-gap during early infancy, and especially in infants born to HIV-infected mothers, when the second dose is only given at ≥14 weeks of age. The choice between a three-dose as a primary-series compared to two-doses followed by a booster-vaccine should ideally be tailored to the local epidemiology of pneumococcal disease in the country where four-doses are not possible. In a setting such as South Africa with a high prevalence (30%) of maternal HIV-infection during pregnancy, the effectiveness of the two-dose schedule at 6 and 14 weeks of age, followed by a booster dose at 9-months in preventing childhood IPD and pneumonia needs to be evaluated independently for HIV-exposed and HIV-unexposed infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and baseline features of participants included in the analysis evaluating the immunogenicity of a 7-valent pneumococcal conjugate vaccine (PCV) following each of three doses.

Variable	Overall	HUU[a]	HEU[b]	ART+[c]	ART−[d]	Group-5[e]
Total number of subjects enrolled	565	119	124	205	104	13
Male sex (%)	266 (47.1)	66 (55.5)	67 (54.0)	87 (42.4)	40 (38.5)	6 (46.2)
Total Race: Black African (%)	515 (91.2)	90 (75.6)	116 (93.5)	196 (95.6)	101 (97.1)	12 (92.3)
Mixed ancestry (%)	50 (8.8)	29 (24.4)	8 (6.5)	9 (4.4)	3 (2.9)	1 (7.8)
Mean age (standard deviation; SD) at time of immunogenicity analysis/vaccine administration in weeks (n = number of observation per cell)						
Pre-vaccine/PCV dose-1[f]	7.36 (1.16)	7.03 (1.03)	7.36 (0.99)	7.53 (1.24)	7.28 (1.15)	8.35 (1.56)
Post dose-1/PCV dose-2	11.45 (1.24)	11.1 (1.12)	11.48 (1.01)	11.61 (1.34)	11.4 (1.27)	12.7 (1.84)
Post dose-2/PCV dose-3	15.53 (1.33)	15.17 (1.21)	15.58 (1.07)	15.68 (1.49)	15.47 (1.3)	16.59 (1.65)
Post dose-3[g]	19.51 (1.29)	19.18 (1.24)	19.53 (1.03)	19.59 (1.32)	19.65 (1.49)	20.73 (1.65)
HIV-1 Viral load at baseline- copies/ml (range)				750,000 (395,500–>750,000)	750,000 (436,500–>750,000)	750,000 (>750,000)
Pre-vaccination median CD^{4+} lymphocyte Count (IQR)[h]				2058 (1619–2058)	2058 (1588–2058)	1613 (1161–1613)
Pre-vaccination mean CD^{4+} lymphocyte % (SD)				35.66 (8.39)	36.91 (9.37)	21.75 (5.84)
One-month post dose-3 median CD^{4+} lymphocyte count at (IQR)i				2212 (1695–2212)	1845 (1110–1845)	1957 (798.5–1957)
One-month post dose-3 mean CD^{4+} % (SD)[i]				40.65 (9.35)	30.1 (8.89)	28.09 (9.66)
Median days (range) to ART initiation relative to PCV1	Not undertaken			0 (−4 to 0)	40 (7.0 to −71.0)[j]	0 days

[a] HUU: HIV non-infected children born to HIV non-infected mothers.

[b] HEU: HIV-uninfected born to HIV-infected mothers.

[c] ART+: HIV-infected children with CD^{4+} ≥ 25% at enrolment randomized to initiate ART immediately.

[d] ART−: HIV-infected children with CD^{4+} ≥25% at enrolment randomized to deferred anti-retroviral treatment (ART) arm.

[e] Group-5: HIV infected children with CD^{4+} cell count <25% started on antiretroviral treatment (ART) at time of first dose of PCV-7.

[f] Blood draw was undertaken just prior to and on the same day of PCV vaccination where applicable.

[g] Includes subjects who received all PCV doses within protocol-defined window periods and available immunogenicity data within 3–6 weeks after 3rd dose of PCV-7.

[h] IQR: interquartile range.

[i] Involve 171, 77 and 8 observations in ART+, ART− and Group-5 children, respectively.

[j] 13 (16.8%) of 77 HIV+/ART− children had been initiated on ART at the time of the immunogenicity analysis.

Table 2

IgG anti-capsular geometric mean concentrations (GMC) and proportion infants with anti-capsular antibody ≥0.35 μg/ml prior to receiving pneumococcal conjugate vaccine (PCV) in HIV-infected and HIV-uninfected infants.

Serotype		HUU[a] *n* = 119	HEU[b] *n* = 124	*p*-Value[c]	ART+[d] *n* = 204–205	*p*-Value[e]	ART–[f] *n* = 104	*p*-Value[g]
4	GMC	0.12 (0.09–0.15)	0.08 (0.07–0.1)	0.006	0.13 (0.11–0.15)	0.772	0.15 (0.12–0.18)	0.354
	≥0.35 μg/ml	24; 20% (14–28)	7; 6% (3–11)	0.001	30; 15% (10–20)	0.094	18; 17% (11–26)	0.318
6B	GMC	0.15 (0.12–0.19)	0.09 (0.07–0.11)	0.003	0.17 (0.14–0.21)	0.419	0.22 (0.16–0.29)	0.072
	≥0.35 μg/ml	38; 32% (24–41)	17; 14% (9–21)	0.001	52; 26% (20–32)	0.227	29; 28% (20–37)	0.498
9V	GMC	0.2 (0.15–0.26)	0.09 (0.07–0.11)	<0.001	0.13 (0.11–0.16)	0.002	0.15 (0.11–0.2)	0.043
	≥0.35 μg/ml	38; 32% (24–41)	16; 13% (8–20)	0.001	35; 17% (12–23)	0.007	20; 19% (13–28)	0.059
14	GMC	1 (0.77–1.29)	0.42 (0.33–0.53)	<0.001	0.86 (0.71–1.05)	0.139	1.05 (0.78–1.42)	0.735
	≥0.35 μg/ml	92; 77% (69–84)	76; 61% (52–69)	0.005	160; 78% (72–83)	0.806	80; 77% (68–84)	0.629
18C	GMC	0.21 (0.16–0.26)	0.1 (0.08–0.12)	<0.001	0.12 (0.1–0.13)	<0.001	0.11 (0.09–0.14)	<0.001
	≥0.35 μg/ml	37; 31% (24–40)	17; 14% (9–21)	<0.001	28; 14% (10–19)	<0.001	16; 15% (10–24)	0.002
19F	GMC	0.62 (0.49–0.8)	0.23 (0.18–0.28)	<0.001	0.48 (0.4–0.57)	0.037	0.57 (0.43–0.75)	0.338
	≥0.35 μg/ml	89; 75% (66–82)	42; 34% (26–43)	<0.001	124; 60% (54–67)	0.008	64; 62% (52–70)	0.029
23F	GMC	0.25 (0.2–0.31)	0.12 (0.1–0.15)	<0.001	0.18 (0.16–0.21)	0.004	0.19 (0.16–0.24)	0.024
	≥0.35 μg/ml	50; 42% (34–51)	22; 18% (12–25)	<0.001	55; 27% (21–33)	0.001	32; 31% (23–40)	0.027

[a] HUU: HIV non-infected children born to HIV non-infected mothers.

[b] HEU: HIV-uninfected born to HIV-infected mothers.

[c] *p*-Value comparing HEU to HUU infants.

[d] ART+: HIV-infected children with CD^{4+} ≥ 25% at enrolment randomized to initiate ART immediately.

[e] *p*-Value comparing ART+ to HUU infants.

[f] ART−: HIV-infected children with CD^{4+} ≥ 25% at enrolment randomized to deferred anti-retroviral treatment (ART) arm.

[g] *p*-Value comparing ART− to HUU children.

Table 3

IgG anti-capsular geometric mean concentrations (GMC) one month following the first, second and third dose of pneumococcal conjugate vaccine (PCV) in HIV-infected and HIV-uninfected infants.

Group	Serotype	Post dose 1	*p*-Valuee	Post dose 2	*p*-Value[f]	Post dose 3	*p*-Value[g]
HUU[a]		*n* = 117	Referent group	*n* = 116	Referent group	*n* = 114	
	4	0.45 (0.36–0.56)		4.43 (3.44–5.70)		6.45 (5.32–7.82)	<0.001
	6B	0.16 (0.13–0.21)		0.24 (0.19–0.30)		1.43 (1.05–1.94)	<0.001
	9V	0.31 (0.26–0.38)		3.84 (3.01–4.91)		5.12 (4.36–6.0)	0.015
	14	0.82 (0.65–1.05)		1.78 (1.48–2.15)		3.6 (2.90–4.47)	<0.001
	18C	0.44 (0.36–0.54)		3.29 (2.61–4.15)		6.02 (5.0–7.25)	<0.001
	19F	0.81 (0.67–0.99)		4.04 (3.24–5.03)		6.97 (5.88–8.27)	<0.001
	23F	0.25 (0.20–0.32)		0.83 (0.65–1.06)		4.09 (3.23–5.19)	<0.001
HEU[b]		*n* = 122		*n* = 121		*n* = 120	
	4	0.42 (0.34–0.53)	0.75	6.21 (5.21–7.41)	0.033	7.99 (7–9.12)	0.024
	6B	0.08 (0.07–0.10)	<0.001	0.24 (0.19–0.30)	0.961	2.6 (2.01–3.37)	<0.001
	9V	0.21 (0.17–0.27)	0.074	5.01 (4.14–6.06)	0.339	6.45 (5.64–7.38)	0.027
	14	0.39 (0.32–0.48)	0.001	1.76 (1.44–2.16)	0.759	4.47 (3.67–5.46)	<0.001
	18C	0.33 (0.26–0.41)	0.321	4.06 (3.24–5.1)	0.703	7.46 (6.50–8.57)	<0.001
	19F	0.44 (0.36–0.55)	0.002	4.96 (3.92–6.27)	0.397	8.47 (7.07–10.14)	<0.001
	23F	0.12 (0.10–0.15)	0.003	1.15 (0.93–1.43)	0.145	6.91 (5.84–8.17)	<0.001
ART+[c]		*n* = 196		*n* = 191		*n* = 169–171	
	4	0.48 (0.39–0.58)	0.83	4.79 (4.0–5.75)	0.463	5.75 (5.02–6.59)	0.059
	6B	0.12 (0.11–0.14)	0.003	0.38 (0.32–0.46)	0.014	2.26 (1.85–2.75)	<0.001
	9V	0.23 (0.19–0.27)	0.038	4.29 (3.56–5.16)	0.777	5.46 (4.80–6.21)	0.041
	14	0.52 (0.45–0.6)	0.001	1.83 (1.56–2.14)	0.999	4.83 (4.09–5.69)	<0.001
	18C	0.36 (0.29–0.44)	0.447	3.9 (3.18–4.79)	0.733	6.06 (5.30–6.92)	<0.001
	19F	0.62 (0.54–0.72)	0.016	4.8 (4.02–5.74)	0.344	7.56 (6.7–8.53)	<0.001
	23F	0.2 (0.16–0.24)	0.214	1.23 (1.0–1.52)	0.057	4.81 (4.01–5.77)	<0.001
ART−[d]		*n* = 91		*n* = 84		*n* = 77	
	4	0.61 (0.45–0.81)	0.207	4.95 (3.32–7.4)	0.438	5.94 (4.41–8.0)	0.178
	6B	0.15 (0.12–0.19)	0.088	0.52 (0.36–0.74)	0.001	3.52 (2.43–5.10)	<0.001
	9V	0.31 (0.24–0.41)	0.793	2.94 (1.83–4.71)	0.133	4.85 (3.62–6.50)	0.019
	14	0.67 (0.54–0.84)	0.086	2.03 (1.51–2.73)	0.526	6.33 (4.84–8.28)	<0.001
	18C	0.46 (0.34–0.62)	0.569	3.92 (2.61–5.87)	0.799	5.2 (3.85–7.03)	0.234
	19F	0.75 (0.61–0.93)	0.199	5.05 (3.65–6.98)	0.272	6.19 (4.87–7.88)	0.146
	23F	0.23 (0.18–0.31)	0.742	1.46 (1.01–2.1)	0.023	5.38 (3.89–7.44)	<0.001

[a] HUU: HIV non-infected children born to HIV non-infected mothers.

[b] HEU: HIV-uninfected born to HIV-infected mothers.

[c] ART+: HIV-infected children with $CD4+ \geq 25\%$ at enrolment randomized to initiate ART immediately.

[d] ART−: HIV-infected children with $CD^{4+} \geq 25\%$ at enrolment randomized to deferred anti-retroviral treatment (ART) arm.

[e] *p*-Value comparing post-dose 1 anticapsular IgG antibody GMC to that of HUU group.

[f] *p*-Value comparing post-dose 2 anticapsular IgG antibody GMC to that of HUU group.

[g] *p*-Value comparing post dose-2 to post dose-3 anticapsular IgG antibody GMC within each group.

Table 4

Proportion of infants with anti-capsular IgG antibody ≥0.35 μg/ml one month following the first, second and third dose of pneumococcal conjugate vaccine (PCV) in HIV-infected and HIV-uninfected infants.

Group	Serotype	Post dose 1 (*n*; % (95% CI)	*p*-Valuee	Post dose 2 (*n*; % (95% CI)	*p*-Value[f]	Post dose 3 (*n*; % (95% CI)	*p*-Value[g]
HUU[a]		*N* = 117	Refer-ent group	*N* = 116	Refer-ent group	*N* = 114	
	4	68; 58% (49–67)		107; 92% (86–96)		112; 98% (94–100)	0.05
	6B	31; 26% (19–35)		43; 37% (29–46)		94; 82% (74–88)	<0.001
	9V	57; 49% (40–58)		109; 94% (88–97)		113; 99% (95–100)	NE[h]
	14	86; 74% (65–81)		113; 97% (93–99)		110; 96% (91–99)	0.706
	18C	70; 60% (51–68)		112; 97% (92–99)		113; 99% (95–100)	0.215
	19F	96; 82% (74–88)		112; 97% (92–99)		113; 99% (95–100)	0.215
	23F	43; 37% (29–46)		93; 80% (72–86)		108; 95% (89–98)	0.003
HEU[b]		*N* = 122		*N* = 121		*N* = 120	
	4	68; 56% (47–64)	0.74	120; 99% (96–100)	0.034	120; 100% (97–100)	NE
	6B	11; 9% (5–15)	<0.001	42; 35% (27–44)	0.522	111; 92% (86–96)	<0.001
	9V	43; 35% (27–44)	0.017	121; 100% (97–100)	0.986	119; 99% (95–100)	NE
	14	73; 60% (51–68)	0.019	115; 95% (90–98)	0.323	118; 98% (94–100)	0.178
	18C	66; 54% (45–63)	0.422	114; 94% (88–97)	0.384	120; 100% (97–100)	NE
	19F	83; 68% (59–76)	0.005	116; 96% (91–98)	0.869	119; 99% (95–100)	NE
	23F	22; 18% (12–26)	0.001	105; 87% (80–92)	0.301	119; 99% (95–100)	NE
ART+[c]		*N* = 196		*N* = 191		*N* = 169–171	
	4	116; 59% (52–66)	0.795	184; 96% (93–98)	0.171	168; 99% (97–100)	0.142
	6B	30; 15% (11–21)	0.007	95; 50% (43–57)	0.094	158; 92% (87–96)	<0.001
	9V	64; 33% (26–40)	0.001	179; 94% (89–96)	0.866	168; 99% (96–100)	0.069
	14	136; 69% (63–75)	0.338	182; 95% (91–98)	0.312	169; 99% (97–100)	0.05
	18C	98; 50% (43–57)	0.115	179; 94% (89–96)	0.3	170; 99% (97–100)	0.037
	19F	135; 69% (62–75)	0.004	183; 96% (92–98)	0.846	169; 100% (98–100)	NE
	23F	47; 24% (18–30)	0.006	151; 79% (73–84)	0.591	164; 96% (92–98)	<0.001
ART−[d]		*N* = 91		*N* = 84		*N* = 77	
	4	61; 67% (57–76)	0.189	76; 90% (82–95)	0.58	75; 97% (91–99)	NE
	6B	18; 20% (13–29)	0.13	50; 60% (49–69)	0.009	68; 88% (79–94)	0.003
	9V	40; 44% (34–54)	0.235	71; 84% (75–91)	0.026	73; 95% (87–98)	NE
	14	70; 77% (67–84)	0.735	77; 92% (84–96)	0.072	75; 97% (91–99)	NE
	18C	49; 54% (44–64)	0.401	75; 89% (81–94)	0.057	72; 94% (86–97)	0.341
	19F	77; 85% (76–91)	0.933	80; 95% (88–98)	0.734	75; 97% (91–99)	NE
	23F	29; 32% (23–42)	0.226	71; 84% (75–91)	0.639	73; 95% (87–98)	0.054

[a] HUU: HIV non-infected children born to HIV non-infected mothers.

[b] HEU: HIV-uninfected born to HIV-infected mothers.

[c] ART+: HIV-infected children with CD^{4+} ≥ 25% at enrolment randomized to initiate ART immediately.

[d] ART−: HIV-infected children with CD^{4+} ≥ 25% at enrolment randomized to deferred anti-retroviral treatment (ART) arm.

[e] *p*-Value comparing post-dose 1 anticapsular IgG antibody GMC to that of HUU group.

[f] *p*-Value comparing post-dose 2 anticapsular IgG antibody GMC to that of HUU group.

[g] *p*-Value comparing post dose-2 to post dose-3 anticapsular IgG antibody GMC within each group.

[h] NE: not evaluable. *p*-Value is not calculable through logistic regression.

Table 5

Opsonophagocytic activity assay (OPA) post-second and third dose of pneumococcal conjugate vaccine in HIV-infected and HIV-uninfected infants.

Group	OPA geometric mean titer (95% CI)				OPA titer ≥8 (95% CI)			
	Post dose 2 GMT (95% CI)	Post dose 3 GMT (95% CI)	*p*-Value[e]	*p*-Value[f]	Post dose 2 *N* % (95% CI)	Post dose 3 *N* % (95% CI)	*p*-Value[e]	*p*-Value[f]
Serotype 9V								
HUU[a]	362 (261–501)	566 (471–681)	0.006	–	100; 93.5% (0.87–0.97)	114; 100% (0.97–1)	NEg	–
HEU[b]	581 (462–729)	610 (497–749)	0.574	0.151	102; 99.0% (0.95–1)	118; 99.2% (0.95–1)	NE	0.108
ART+[c]	246 (190–318)	724 (623–843)	<0.001	0.09	165; 92.7% (0.88–0.96)	171; 99.4% (0.97–1)	0.037	0.501
ART−[d]	178 (114–279)	331 (219–500)	0.021	0.012	71; 88.8% (0.8–0.94)	68; 88.3% (0.79–0.94)	0.484	0.136
Serotype 19F								
HUU	73 (55–97)	365 (303–439)	<0.001	-	98; 86.0% (0.78–0.91)	113; 99.1% (0.95–1)	NE	–
HEU	97 (73–128)	283 (230–349)	<0.001	0.299	108; 90.0% (0.83–0.94)	115; 95.8% (0.91–0.98)	0.054	0.724
ART+	85 (68–107)	312 (267–365)	<0.001	0.429	167; 89.3% (0.84–0.93)	169; 98.3% (0.95–0.99)	NE	0.591
ART−	69 (47–101)	149 (102–219)	<0.001	0.909	73; 86.9% (0.78–0.93)	68; 88.3% (0.79–0.94)	0.372	0.953
Serotype 23F								
HUU	35 (24–50)	1755 (1311–2350)	<0.001	–	77; 67.5% (0.58–0.75)	110; 97.3% (0.92–0.99)	0.001	–
HEU	97 (71–133)	2678 (2133–3363)	<0.001	<0.001	107; 89.2% (0.82–0.94)	118; 98.3% (0.94–1)	NE	<0.001
ART+	98 (72–135)	1309 (1017–1686)	<0.001	<0.001	143; 76.9% (0.7–0.82)	163; 95.3% (0.91–0.98)	0.001	0.063
ART−	67 (42–108)	758 (468–1227)	<0.001	0.007	63; 75.9% (0.66–0.84)	69; 89.6% (0.81–0.95)	0.028	0.146

[a] HUU: HIV non-infected children born to HIV non-infected mothers.

[b] HEU: HIV-uninfected born to HIV-infected mothers.

[c] ART+: HIV-infected children with $CD^{4+} \geq 25\%$ at enrolment randomized to initiate ART immediately.

[d] ART−: HIV-infected children with $CD^{4+} \geq 25\%$ at enrolment randomized to deferred anti-retroviral treatment (ART) arm.

[e] *p*-Value comparing post dose 2 and post dose-3 within each group.

[f] *p*-Value comparing study group to HUU infants.

[g] NE: not evaluable. *p*-Value is not calculable through logistic regression.