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# Antibody Persistence and Immunologic Memory after Sequential Pneumococcal Conjugate and Polysaccharide Vaccination in HIV-Infected Children on Highly Active Antiretroviral Therapy

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## Abstract

**Background—**The capacity of pneumococcal vaccination to confer memory in HIV-infected children is critical for durable protection.

**Methods—**HIV-infected children 2–<19 years administered two doses of pneumococcal conjugate vaccine (PCV7) and one dose of polysaccharide vaccine (PPV) on HAART were randomized four-five years later to receive a PCV7 or PPV booster. Total and high avidity antibodies to serotypes 1 (PPV) and 6B and 14 (PCV7 and PPV) were determined by ELISA. Memory was defined as persistence of ≥0.5 mcg/mL of serotype-specific antibody on day 0 or



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Conflict of Interest

Mark J. Abzug: no commercial or other association that poses a conflict of interest
Lin Ye Song: no commercial or other association that poses a conflict of interest
Myron J. Levin is a consultant to and shares intellectual property with Merck, Sharpe & Dohme.
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change from <0.5 mcg/mL to ≥0.5 mcg/mL between day 0 and week 1, or, ≥4-fold antibody rise between day 0 and week 1.

**Results—**Prior to boosting, four to five years after the previous PCV7-PCV7-PPV series, geometric mean concentrations (GMCs) were 0.46 mcg/mL (serotype 1), 1.31 mcg/mL (serotype 6B), and 1.47 mcg/mL (serotype 14), with concentrations ≥0.5 mcg/mL in 41% (serotype 1) to 82% (serotypes 6B and 14). Memory based on antibody concentration ≥0.5 mcg/mL before or 1 week after boosting with PCV7 or PPV was demonstrated in 42–61% for serotype 1 and 87–94% for serotypes 6B and 14, with lower rates based on day 0 to week 1 ≥4-fold antibody rise (serotype 1, 3–13%; serotype 6B, 13–31%; serotype 14, 29–53%). Antibody concentrations post-boosting were greater following PCV7 than PPV for serotypes 6B and 14. Ratios of highly avid to total antibody pre- and post-boosting were 0.5–0.8. Predictors of memory included higher CD4% (nadir before HAART and at P1024 and P1061s entry), CD19% (at P1024 and P1061s entry), and antibody response after the PCV7-PCV7-PPV primary series and lower viral load (at P1024 and P1061s entry) and age.

**Conclusions—**Protective antibody concentrations, high avidity, and booster responses to PCV7 or PPV indicative of memory were present four-five years after PCV7-PCV7-PPV in HIV-infected children on HAART.

### Keywords

pneumococcal; vaccine; memory; HIV; children

## Introduction

Infections caused by *Streptococcus pneumoniae* remain an important problem in HIV-infected children and adults, even where highly active antiretroviral therapy (HAART) is widely used [1–4]. Pneumococcal conjugate vaccines (PCVs) prevent invasive pneumococcal disease in HIV-infected children and adults [5–6]. A 3-dose series of 9-valent PCV administered to HIV-infected infants in South Africa reduced invasive disease caused by vaccine serotypes by 65%, although efficacy was lower than the 83% efficacy in HIV-uninfected children [5, 7]. After a mean of six years, efficacy in these young HIV-infected children fell to 39%, compared with 78% efficacy in HIV-uninfected children. Serotype-specific antibody levels were lower in HIV-infected children compared with HIV-uninfected counterparts before and after a subsequent PCV booster dose. Similarly, among HIV-infected adults in Malawi with a prior pneumococcal infection, efficacy of 7-valent PCV decreased from 85% in the first year after a 2-dose series to 25% in subsequent years [6]. These observations suggest waning protection following PCV in HIV-infected children and adults. In these studies, most subjects were not receiving antiretroviral therapy at primary vaccination or during follow-up. Whether HAART-associated immune preservation and/or reconstitution affect development of memory and persistence of protection is critical to understanding optimal timing of pneumococcal immunization, its long-term impact on HIV-infected children, and need for booster doses.

International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) study P1024 evaluated the immunogenicity of 2 doses of 7-valent PCV followed by 1 dose of 23-valent pneumococcal polysaccharide vaccine (PPV) in HIV-infected children on HAART. Vaccination was immunogenic, with antibody responses comparable to those of healthy children and generally higher than in antiretroviral-naïve South African infants [8]. This report focuses on a substudy of P1024, IMPAACT P1061s, which evaluated persistence of antibody and memory 4–5 years following PCV7-PCV7-PPV vaccination.

## Materials and Methods

### Study population

HIV-infected children 2–<19 years old were eligible for P1024 if they fit into immunologic strata based on nadir CD4% prior to HAART and CD4% at screening: stratum 1, <15% and <15%; stratum 2, <15% and ≥15%; stratum 3, 15%–≤25% and ≥15%; and stratum 4, ≥25% and ≥25%. Additional inclusion criteria included perinatal infection (strata 2–4 only), stable HAART regimen (≥3 antiretrovirals from ≥2 classes) for ≥6 months (≥3 months for stratum 1), and an HIV RNA PCR (Roche Amplicor Monitor Assay) <30,000 copies/mL (<60,000 copies/mL for stratum 1), and no prior PCV. Subjects received PCV7 at entry and 8-weeks and PPV at 16-weeks. Subjects who enrolled in P1024 June 2001–March 2002 were eligible for P1061s, which enrolled February 2006–August 2006 at 26/39 sites that participated in P1024. Subjects were maintained in the same strata to which they were classified in P1024.

### Study protocol

Informed consent was obtained and human experimentation guidelines of the US Department of Health and Human Services and participating institutions were followed. Subjects who received two doses of PCV7 and one dose of PPV in P1024 without ≥ grade 3 adverse events or allergic reactions related to PCV7 or PPV and had not received additional doses of either vaccine since the conclusion of P1024 qualified to receive one dose of PCV7 (Pneumococcal 7-Valent Conjugate Vaccine, Prevnar; Wyeth-Lederle Vaccines; 0.5 mL intramuscular) or PPV (Polyvalent Pneumococcal Vaccine, PNEUMOVAX 23; Merck & Co.; 0.5 mL intramuscular) at P1061s entry, based on 1:1 random assignment within strata. Hepatitis B virus and measles-mumps-rubella vaccines were also administered [9–10]. Pneumococcal antibody concentrations were measured at entry and 1 and 4 weeks post-booster, and plasma HIV RNA viral load (VL) and lymphocyte subsets were measured at entry.

### Laboratory assays and immunologic definitions

IgG antibodies to pneumococcal serotypes 1 (PPV-containing only) and 6B and 14 (PCV7- and PPV-containing) were determined by ELISA [8]. These serotypes were selected because serotype 6B is among the least immunogenic serotypes and might be sensitive to differences between PCV7 and PPV and among immunologic strata; serotype 14 represents the most common serotype causing invasive disease in U.S. children prior to PCV7; and protection against serotype 1 waned quickly in South African HIV-infected children, suggesting the need to understand antibody persistence for this serotype [11]. Serotype-specific antibody avidity was determined using a modification employing 0.5M NaSCN as a chaotropic agent to elute low affinity antibody [12]. Control serum (SF89, Dr. Carl Frasch, Food and Drug Administration, Bethesda, MD) was used as the standard to determine serotype-specific antibody concentrations.

A uniform threshold for assessing antibody persistence and memory to each serotype was used as suggested by World Health Organization guidance [13–14]. Although a concentration of 0.35 mcg/mL is considered a correlate of protection by licensing agencies, we selected a threshold concentration of 0.5 mcg/ml to reflect higher pre-vaccination antibody concentrations and poorer antibody function in pediatric AIDS patients that suggest that greater antibody quantities may be necessary for protection in HIV-infected children against invasive infection and pneumonia [15]. Correlation of ELISA antibody at this level with opsonophagocytic activity for serotypes 6B and 14 has been demonstrated in HIV-infected children [14].

Immunologic memory was defined as: (1) antibody persistence with ≥0.5 mcg/mL of serotype-specific antibody on day 0 or change from <0.5 mcg/mL to ≥0.5 mcg/mL between day 0 and week 1, or, (2) ≥4-fold antibody rise between day 0 and week 1. Combined response (memory or primary response) was defined as (1) antibody concentration ≥0.5 mcg/mL at day 0, week 1, or week 4, or, (2) ≥4-fold rise in antibody concentration between day 0 and week 1 or day 0 and week 4 (Supplementary Text and Supplementary Table 1). Avidity results were expressed as the avidity ratio, the proportion of total ELISA antibody that remained bound after elution.

### Statistical analysis

All subjects who received 2 doses of PCV7 and 1 dose of PPV in P1024, had neither vaccine between the last P1024 visit and P1061s entry, and had pneumococcal serologies at P1061s entry were included in analyses of antibody persistence. Timepoints included weeks -212, -188, and -140 relative to P1061s entry (P1024 timepoints corresponding to 8, 32, and 80 weeks after the conclusion of the PCV7-PCV7-PPV regimen) and P1061s entry (week 0). Subjects who received a PCV7 or PPV booster in P1061s and had serologic results at entry, week 1 (6–13 days), and week 4 (25–36 days) were included in analyses of memory. Because only one P1061s subject was in immune stratum 1, this subject was included in analyses in which strata were combined but was not included in comparisons among strata. Comparisons utilized Fisher's Exact test for categorical variables; Kruskal-Wallis, Wilcoxon Rank Sum, and Wilcoxon Signed Rank tests for continuous variables; and McNemar's test for comparison of response rates between timepoints. Univariate logistic regression analyses assessing predictors of memory focused on parameters predictive of PCV7-PCV7-PPV response in P1024.

## Results

### Population characteristics

One hundred one of 224 eligible P1024 subjects enrolled in P1061s. Forty-three received PCV7 and 41 received PPV. Eleven did not qualify for PCV7 or PPV because they had received PPV between P1024 and P1061s and six due to PCV7- or PPV-associated adverse events in P1024. Sixty-seven of 84 vaccine recipients had data available at each timepoint for inclusion in analyses of memory (Table 1). Only 5/67 had a CD4% that would no longer have placed them in their original P1024 strata. Higher immune stratum was associated with younger age ($p = 0.02$, PCV7 recipients), higher nadir CD4% ($p < 0.001$, PCV7 and PPV), higher P1024 CD4% ($p < 0.01$, PPV), lower P1024 VL ($p = 0.05$, PPV), greater P1061s CD4% ($p < 0.01$, PPV), and lower P1061s VL. Median time from conclusion of the P1024 PCV7-PCV7-PPV regimen to P1061s entry was 4.2 years.

P1024 baseline characteristics and serologic results were similar between subjects who qualified for P1061s memory analyses and the remainder of the P1024 PCV7/PPV analysis group except for trends toward better virologic control at P1024 entry among subjects in P1061s analyses (VL <400 copies/mL, 73% v. 56%; 401–5000 copies/mL, 12% v. 22% ; >5000 copies/mL, 15% v. 22%; p=0.06) and a higher median P1024 CD4 count in the P1061s subset ($940/mm^3$ v. $888/mm^3$, $p = 0.06$), with no difference in median P1024 CD4% (34% v. 33%, $p = 0.28$).

### Antibody persistence

Antibody concentrations for serotypes 1, 6B, and 14 at each timepoint after the P1024 PCV7-PCV7-PPV regimen (week -212 relative to P1061s entry) until P1061s entry (week 0) were significantly lower than the previous timepoint ($p \leq 0.03$), except for the week -188 to week -140 interval for serotypes 6B and 14 (Figure 1). Concentrations declined more rapidly

between weeks -212 to -188 than between weeks -188 to -140 and weeks -140 to 0 ($p < 0.01$, paired signed rank test). Among the 3 serotypes, there were no overall differences in rates of antibody decay between weeks -212 and 0. Curves for each immune stratum mirrored overall curves for each serotype. GMCs generally varied directly with stratum, with differences lessening as the interval from PCV7-PCV7-PPV increased. The slope of antibody fall between week -212 and week 0 was greater with increasing stratum for serotype 6B ($p = 0.01$, Kruskal-Wallis test).

GMCs at P1061s entry exceeded 0.5 mcg/mL for serotypes 6B and 14, but not serotype 1, and exceeded these subjects' GMCs prior to P1024 entry, for all 3 serotypes: serotype 1, 0.46 mcg/mL v. 0.26 mcg/mL; serotype 6B, 1.31 mcg/mL v. 0.75 mcg/mL; serotype 14, 1.47 mcg/mL v. 0.32 mcg/mL ($p \leq 0.001$, paired signed rank test). GMCs for each of immune strata 2–4 for serotypes 6B and 14, but only for stratum 4 for serotype 1, were ≥0.5 mcg/mL at P1061s entry. The GMC at P1061s entry was significantly higher with increasing immune stratum for serotype 14 only ($p = 0.04$, Kruskal-Wallis test). The proportions of subjects with antibody concentrations ≥0.5 mcg/mL at P1061s entry were 41% for serotype 1 and 82% for serotypes 6B and 14.

### Antibody concentrations after P1061s vaccination

Among all strata combined, serotype 1 GMCs increased at weeks 1 and 4 only in PPV recipients, as expected, whereas GMCs increased at weeks 1 and 4 for serotypes 6B and 14 in PCV7 and PPV recipients (Table 2). The GMC for serotype 1 four weeks after boosting with PPV was similar to the GMC of 1.5 mcg/mL eight weeks after P1024 PCV7-PCV7-PPV vaccination, while for serotypes 6B and 14, GMCs four weeks after boosting with PCV7 or PPV exceeded GMCs of 3.23 and 3.55 mcg/mL, respectively, measured eight weeks after PCV7-PCV7-PPV. PCV7 recipients attained higher GMCs than PPV recipients for serotype 14 at weeks 1 and 4, with a similar pattern within immune strata. GMCs were generally greater in higher immune strata, with significant differences for serotype 14. Antibody concentrations of PCV7 and PPV recipients (combined) at week 1 correlated negatively with age for serotypes 6B (Rho = −.30, P = .01) and 14 (Rho = −.25, P = .04).

The proportion with antibody concentrations ≥0.5 mcg/mL for serotype 1 increased only among PPV recipients, as expected, from 39% to 61% at week 1 and 94% at week 4. For serotypes 6B and 14, baseline rates of antibody concentrations ≥0.5 mcg/mL were already 72–84%, increasing in PCV7 and PPV recipients to 86–94% and 90–100% at weeks 1 and 4, respectively.

### Antibody avidity

Avidity ratios ranged from 0.3–0.8 for serotype 1, 0.5–0.9 for serotype 6B, and 0.6–0.9 for serotype 14, with no consistent differences among study timepoints, PCV7 v. PPV booster recipients, or strata.

### Memory responses

The proportions with memory based on antibody concentration ≥0.5 mcg/mL at entry or week 1 were lower for serotype 1 (42%, 61%) compared with serotypes 6B and 14 (87–94%), for which rates were similar following PCV7 or PPV booster (Table 3). Memory responses based on ≥4-fold rise at week 1 were substantially lower than those based on antibody concentration ≥0.5 mcg/mL, with the highest rates for serotype 14. Memory based on 4-fold rise was observed for serotypes 6B and 14 more frequently following PCV7 booster than PPV booster. Trends within immune strata mirrored overall trends. All subjects manifesting memory based on ≥4-fold rise at week 1 had antibody concentrations ≥0.5 mcg/mL at week 1.

### Predictors of memory

Memory was associated with higher CD4% (nadir before HAART, P1024 screening, P1061s entry) and CD19% (P1024 and P1061s entry), younger age, lower P1024 and P1061s VL, and greater antibody concentration eight weeks after P1024 vaccination (Table 4).

### Safety

No ≥ grade 3 adverse events related to vaccination were observed.

## Discussion

Long-term protection against encapsulated bacteria requires sustained antibody levels, in addition to persistence of memory B cells [16–17]. A strong correlation between persistence of antibody and frequency of memory B cells has been observed, suggesting that memory is implied by persistence of antibody [17]. We used definitions of memory that included antibody persistence and anamnestic responses. Antibody concentrations at P1061s entry remained greater than at P1024 entry for all three serotypes, more than 4 years after PCV7-PCV7-PPV vaccination. For serotypes 6B and 14, present in PCV7 and PPV, GMCs exceeded 0.5 mcg/mL, while for serotype 1, present only in PPV, the GMC was slightly below this threshold. Antibody levels ≥0.5 mcg/mL persisted in 82% of subjects for PCV7-containing serotypes and in 42% for serotype 1. Booster vaccination with PCV7 or PPV increased GMCs and the proportion with antibody concentration ≥0.5 mcg/mL (except for serotype 1 in PCV7 recipients) at one week. GMCs 4 weeks after PCV7 or PPV for serotypes 6B and 14 were 1.5–3.0-fold higher than peak concentrations following previous PCV7-PCV7-PPV, consistent with booster responses. In contrast, the GMC after PPV boosting for serotype 1 was only comparable to that after the PCV7-PCV7-PPV regimen. Although U.S. guidelines recommending pneumococcal vaccination for HIV-infected children precluded having a control group of previously unvaccinated, HIV-infected children, our finding that antibody concentrations correlated inversely with age suggests that memory, rather than age-related immune maturation, was responsible for higher GMCs for serotypes 6B and 14 after boosting compared with GMCs after the previous vaccine series. Boosting with PCV7 yielded higher GMCs than with PPV for serotypes in both vaccines, in contrast to studies in healthy children [18], while comparably high proportions with antibody concentration ≥0.5 mcg/mL were achieved for these serotypes following either vaccine. Among subjects who received a PPV booster, despite the absence of an anamnestic response for serotype 1, a high percentage achieved antibody concentrations ≥0.5 mcg/mL for all 3 serotypes by week 4.

A lower proportion with persistence of antibody concentrations ≥0.5 mcg/mL, an increase in GMC after boosting to the same level achieved after previous vaccination, and a lower rate of memory for serotype 1 are consistent with its presentation as an unconjugated polysaccharide in PPV and the experience that PPV has modest immunogenicity, poor durability, and inconsistent efficacy in HAART-treated HIV-infected subjects [8]. In contrast, a large majority demonstrated antibody persistence and memory based on antibody concentration ≥0.5 mcg/mL at entry or week 1 for serotype 6B, a traditionally poor immunogen, and serotype 14. Memory for these serotypes was comparable to memory following measles vaccination (85%) in P1024/P1061s, but greater than for hepatitis B vaccine (45%) [9–10]. Antibody, in subjects boosted with PCV7 or PPV, was predominantly high avidity antibody, which is associated with memory and functional immunity [19–20]. Rates of memory were more modest with the 4-fold response criterion, similar to measles and hepatitis B vaccination, perhaps because of relatively high antibody concentrations pre-boosting [9–10, 21].

Antibody persistence and memory for PCV7 serotypes in children vaccinated while on HAART contrasts with waning efficacy and seropositivity and modest boosting after PCV vaccination in the absence of HAART in HIV-infected South African children [5]. Previous studies of HIV-infected children on HAART demonstrated low responses and short-lived antibody persistence following primary PCV7 vaccination and low responses and declining avidity after a PCV7 booster, mirroring findings in HIV-infected adults [14, 22–23]. Depletion of memory cells by previous PPV vaccination was proposed as a cause of impaired induction of memory [22]. In contrast, subjects in P1024/P1061s manifested memory (and lacked hyporesponsiveness) despite 75% having received ≥1 PPV doses prior to PCV7 [8]. Experience with *Haemophilus influenzae* type b conjugate vaccine in HIV-infected children is similarly conflicting [24–25]. Disparate results may reflect dissimilarities in HIV VL and CD4 profiles, vaccination schedules, age, and study endpoints [26]. Although several studies suggest that reductions in number or function of memory B cell subsets in HIV-infected individuals may limit memory [27–30], the present study suggests that a PCV7- and PPV-containing vaccine regimen does elicit memory in older HIV-infected children on HAART who have favorable CD4 counts and low HIV VL.

Higher CD4% (prior to HAART, at primary PCV7 vaccination, or at boosting) and lower VL (at primary PCV7 vaccination or boosting) were predictive of memory, similar to HBV vaccine-induced memory, but contrasting with live-virus measles vaccine, for which HIV VL, but not CD4 measures, was predictive. Greater antibody concentration after the PCV7-PCV7-PPV series was a strong predictor of memory, similar to findings for HBV and measles vaccines [9–10].

Antibody boosting due to carriage of serotypes 6B and/or 14 is a possible alternative explanation for antibody persistence we observed. This possibility is mitigated, however, by low pneumococcal carriage rates in adolescents and declines in carriage of PCV7 serotypes following introduction of universal infant/toddler PCV7 vaccination. Other possible study limitations include use of ELISA rather than functional antibody responses [24] and that protective antibody concentrations established in healthy populations may overestimate protection in HIV-infected children [31]. Nevertheless, we found antibody to have high avidity, suggesting adequate quality. The definition of memory based on ≥4-fold antibody increase one week after boosting likely underestimated memory if kinetics are delayed in HIV-infected children. Finally, power may have been limited by the number of subjects, chance associations may have occurred due to multiple comparisons, and exclusion of subjects with high HIV VL may limit generalizability.

Pneumococcal infections continue to be an important threat to HIV-infected children, even in the HAART era [1]. Whereas previous studies failed to demonstrate sustained immunogenicity and efficacy of PPV or PCV in HIV-infected children, our findings suggest that a PCV- and PPV-containing regimen in combination with HAART results in memory that persists at least 4–5 years and is likely to provide durable protection against invasive pneumococcal disease.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

| | |
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| **PCV** | pneumococcal conjugate vaccine |
| **PPV** | pneumococcal polysaccharide vaccine |
| **VL** | viral load |

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## Highlights

- HIV-infected children were studied following pneumococcal vaccination on HAART
- Subjects received 2 conjugate (PCV) and 1 polysaccharide (PPV) vaccine doses
- 4–5 years later, most had protective antibody concentrations for PCV serotypes
- Antibody responses following a PCV or PPV booster were indicative of memory
- Antibody measured was primarily high avidity antibody

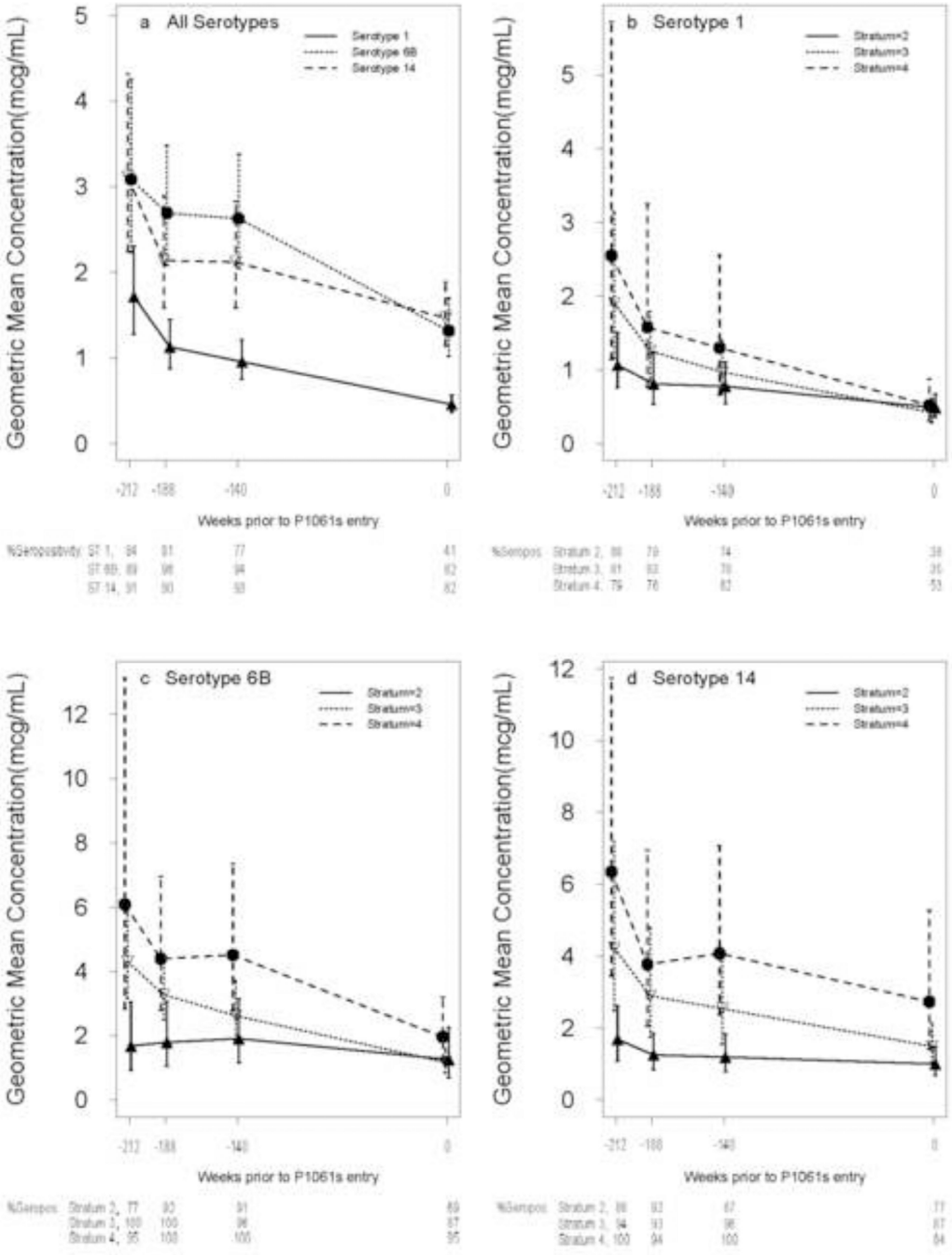


**Figure 1.**

Persistence of antibody between P1024 and P1061s. Geometric mean concentrations and confidence intervals are shown for each of the three serotypes evaluated. Timepoints are at weeks -212, -188, and -140 relative to P1061s entry (8, 32, and 80 weeks after the conclusion of the PCV7-PCV7-PPV regimen in P1024) and at P1061s entry (week 0; a median of 220 weeks after the conclusion of the PCV7-PCV7-PPV series at P1024 week 16). Panel (a) depicts all immune strata combined for the three serotypes and panels (b) – (d) show the immune strata separately for each serotype. Immune stratum 1, which contained only one subject, is excluded from panels (b) – (d). Seventy-nine subjects were assessed at week -212, 73 at week -188, 70 at week -140, and 79 at week 0. The percent with antibody

concentration ≥0.5 mcg/mL (% Seropos) at each timepoint are displayed below panel (a) for the three serotypes (STs; all immune strata combined) and below panels (b) – (d) for each immune stratum (excluding stratum 1). Note: the y-axis scale in panels (a) and (b) extends to 5 mcg/mL, while the y-axis scale in panels (c) and (d) extend to 12 mcg/mL.

## Table 1

Characteristics of the analyzed population.

| Parameter[a] (%, except as noted) | Pneumococcal Conjugate Vaccine 7 | | | | | Pneumococcal Polysaccharide Vaccine | | | | | P-Value[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | All Subjects | Immune Stratum | | | | All Subjects | Immune Stratum | | | | |
| | | 1 | 2 | 3 | 4 | | 1 | 2 | 3 | 4 | |
| N | 36 | 0 | 14 | 14 | 8 | 31 | 1 | 10 | 12 | 8 | |
| Age | | | | | | | | | | | |
| Median, years | 13.8 | NA[c] | 15.5 | 14.2 | 10.8 | 14.6 | 21.9 | 15.1 | 13.4 | 12.8 | 0.55 |
| Range, years | 8.3–21.8 | | | | | 8.5–21.9 | | | | | |
| Interquartile range, years | 12.0–15.8 | | | | | 11.1–16.6 | | | | | |
| Male sex | 42 | NA | 36 | 50 | 38 | 55 | 0 | 60 | 50 | 63 | 0.33 |
| Race/ethnicity | | | | | | | | | | | 0.78 |
| White Non-Hispanic | 17 | NA | 21 | 14 | 13 | 10 | 0 | 0 | 25 | 0 | |
| Black Non-Hispanic | 61 | NA | 50 | 79 | 50 | 65 | 100 | 80 | 42 | 75 | |
| Hispanic | 22 | NA | 29 | 7 | 38 | 26 | 0 | 20 | 33 | 25 | |
| Other | 0 | NA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| CDC clinical classification | | | | | | | | | | | 0.39 |
| N (not symptomatic) | 6 | NA | 0 | 7 | 12 | 13 | 0 | 0 | 33 | 0 | |
| A (mildly symptomatic) | 22 | NA | 21 | 14 | 38 | 35 | 0 | 40 | 33 | 38 | |
| B (moderately symptomatic) | 47 | NA | 36 | 57 | 50 | 32 | 0 | 30 | 17 | 62 | |
| C (severely symptomatic) | 25 | NA | 43 | 21 | 0 | 19 | 100 | 30 | 17 | 0 | |
| Pre-HAART Nadir CD4% | | | | | | | | | | | |
| Median | 16 | NA | 11 | 18 | 30 | 18 | 4 | 9 | 18 | 32 | 0.67 |
| <15% | 39 | NA | 100 | 0 | 0 | 35 | 100 | 100 | 0 | 0 | 0.95 |
| 15%–<25% | 39 | NA | 0 | 100 | 0 | 39 | 0 | 0 | 100 | 0 | |
| ≥25% | 22 | NA | 0 | 0 | 100 | 26 | 0 | 0 | 0 | 100 | |
| P1024 Screening CD4% | | | | | | | | | | | |
| Median | 33 | NA | 31 | 33 | 40 | 35 | 12 | 28 | 38 | 37 | 0.88 |
| <15% | 0 | NA | 0 | 0 | 0 | 3 | 100 | 0 | 0 | 0 | 0.33 |
| 15–<25% | 14 | NA | 29 | 7 | 0 | 6 | 0 | 20 | 0 | 0 | |
| ≥25% | 86 | NA | 71 | 93 | 100 | 90 | 0 | 80 | 100 | 100 | |
| P1024 HIV RNA level | | | | | | | | | | | |

| Parameter[a] (%, except as noted) | Pneumococcal Conjugate Vaccine 7 | | | | | Pneumococcal Polysaccharide Vaccine | | | | | P-Value[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | All Subjects | Immune Stratum | | | | All Subjects | Immune Stratum | | | | |
| | | 1 | 2 | 3 | 4 | | 1 | 2 | 3 | 4 | |
| ≤400 copies/mL | 78 | NA | 57 | 93 | 88 | 68 | 0 | 50 | 75 | 88 | 0.63 |
| 401–5000 copies/mL | 11 | NA | 21 | 0 | 13 | 13 | 0 | 10 | 17 | 13 | |
| >5000 copies/mL | 11 | NA | 21 | 7 | 0 | 19 | 100 | 40 | 8 | 0 | |
| P1061s CD4% | | | | | | | | | | | |
| Median | 33 | NA | 33 | 29 | 35 | 34 | 0 | 29 | 36 | 38 | 0.31 |
| <15% | 8 | NA | 0 | 21 | 0 | 10 | 100 | 20 | 0 | 0 | 1.00 |
| 15–25% | 11 | NA | 14 | 14 | 0 | 13 | 0 | 20 | 17 | 0 | |
| ≥25% | 81 | NA | 86 | 64 | 100 | 77 | 0 | 60 | 83 | 100 | |
| P1061s HIV RNA level | | | | | | | | | | | |
| ≤400 copies/mL | 58 | NA | 57 | 57 | 63 | 74 | 0 | 60 | 92 | 75 | 0.34 |
| 401–5000 copies/mL | 22 | NA | 21 | 14 | 38 | 10 | 0 | 20 | 8 | 0 | |
| >5000 copies/mL | 19 | NA | 21 | 29 | 0 | 16 | 100 | 20 | 0 | 25 | |
| Interval, P1024 week 16 (PPV dose) to P1061s entry | | | | | | | | | | | |
| Median, years | 4.3 | NA | 4.2 | 4.3 | 4.2 | 4.2 | 4.1 | 4.3 | 4.2 | 4.1 | 0.20 |
| Range, years | 4.0–4.8 | | | | | 3.8–4.5 | | | | | |
| Percent not receiving | | | | | | | | | | | |
| HAART at P1061s entry | 11 | NA | 7 | 14 | 12 | 6 | 100 | 0 | 0 | 12 | 0.68 |

Note: N = number of subjects in each subgroup.

[a] Data are percentage of subjects, unless otherwise indicated.

[b] Comparison of subjects who received pneumococcal conjugate vaccine (immune strata combined) v. subjects who received pneumococcal polysaccharide vaccine (immune strata combined).

[c] Not applicable.

## Table 2

Geometric mean antibody concentrations and percentage with antibody levels ≥0.5 mcg/mL before and after booster vaccination in P1061s.

| ST | Week | Pneumococcal Conjugate Vaccine 7 (PCV7) | | | | | | | | Pneumococcal Polysaccharide Vaccine (PPV) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Subject Group | | | | | | | | Subject Group | | | | | | | |
| | | All (36) | 2 (14) | 3 (14) | 4 (8) | All (36) | 2 (14) | 3 (14) | 4 (8) | All (31) | 2 (10) | 3 (12) | 4 (8) | All (31) | 2 (10) | 3 (12) | 4 (8) |
| | | GMC (95% CI) | | | | %≥ 0.5 mcg/mL (95% CI) | | | | GMC (95% CI) | | | | % ≥ 0.5 mcg/mL (95% CI) | | | |
| 1 | 0 | 0.5 (0.3–0.7) | 0.6 (0.3–1.0) | 0.4 (0.2–0.8) | 0.6 (0.2–1.4) | 42 (26–59) | 43 (21–69) | 29 (10–58) | 63 (29–89) | 0.4 (0.3–0.6) | 0.4 (0.3–0.7) | 0.4 (0.2–0.7) | 0.6 (0.2–1.8) | 39 (23–57) | 30 (9–62) | 33 (12–65) | 63 (29–89) |
| | 1[a] | 0.5 (0.3–0.7) | 0.5 (0.3–0.9) | 0.5 (0.2–0.9)[b] | 0.5 (0.2–1.2) | 39 (24–56) | 36 (15–63) | 29 (10–58) | 63 (29–89) | 0.8 (0.6–1.1)[c] | 0.6 (0.3–0.9) | 0.9 (0.5–1.6)[b,c] | 1.0 (0.3–2.9)[c] | 61[d] (43–77) | 50 (22–78) | 67 (35–88) | 75 (35–95) |
| | 4[e] | 0.6 (0.4–0.8)[b] | 0.7 (0.4–1.2) | 0.5 (0.3–1.0)[b,c,f] | 0.5 (0.2–1.1) | 53[g] (35–68) | 50 (23–77) | 50[g] (23–77) | 63 (29–89) | 1.5 (1.1–2.1)[b,c,f] | 0.9 (0.6–1.4)[f] | 1.9 (1.2–3.1)[b,c,f] | 2.2 (0.8–5.7)[c,f] | 94[d,g,h] (80–99) | 90[h] (56–99) | 100[g] (76–100) | 88 (50–99) |
| 6B | 0 | 1.1 (0.7–1.7) | 0.9 (0.4–2.0) | 1.0 (0.5–2.0) | 1.7 (0.7–4.0) | 72 (56–86) | 57 (31–79) | 71 (42–90) | 100 (65–100) | 1.6 (1–2.5) | 2.0 (0.6–6.2) | 1.2 (0.8–2.0) | 2.0 (0.6–7.2) | 84 (67–93) | 80 (44–96) | 92 (65–100) | 75 (35–95) |
| | 1 | 2.7 (1.8–4.3)[c] | 1.8 (0.9–3.4)[c] | 2.5 (1.1–5.6)[c] | 7.0 (2.8–17.4)[c] | 86 (72–94) | 79 (50–94) | 86 (58–97) | 100 (65–100) | 3.0 (1.7–5.1)[c] | 2.0 (0.6–6.6) | 2.9 (1.4–6.1)[c] | 6.0 (1.5–23.1)[c] | 87 (71–95) | 80 (44–96) | 92 (65–100) | 88 (50–99) |
| | 4 | 6.9 (4.6–10.4)[c,f] | 5.8 (3.1–10.8)[c,f] | 5.1 (2.5–10.4)[c,f] | 16.3 (6.5–40.6)[c,f] | 97[h] (86–100) | 100 (77–100) | 93 (69–100) | 100 (65–100) | 4.9 (2.9–8.4)[c,f] | 2.7 (0.7–10.0)[c] | 6.7 (3.7–12.2)[c,f] | 7.9 (2.3–27.4)[c,f] | 90 (75–97) | 80 (44–96) | 100 (76–100) | 88 (50–99) |
| 14 | 0 | 1.6 (1.1–2.3) | 1.3 (0.7–2.7) | 1.4 (0.8–2.3) | 2.7 (1.0–7.4) | 83 (68–92) | 79 (50–94) | 86 (58–97) | 88 (50–99) | 1.3 (0.9–1.9) | 0.8 (0.5–1.4) | 1.3 (0.8–2.2) | 2.5 (0.8–8.4) | 84 (67–93) | 80 (44–96) | 92 (65–100) | 88 (50–99) |
| | 1 | 6.5 (4.2–10.2)b,c | 4.5 (1.9–10.4)[c,i] | 6.2 (2.9–13.3)[c,i] | 13.4 (6.8–26.5)[c,i] | 94 (81–99) | 93 (69–100) | 93 (69–100) | 100 (65–100) | 3.0 (1.9–4.7)[b,c] | 1.6 (0.9–3)[c,i] | 3.3 (1.5–7.5)[c,i] | 6.6 (2.3–19.4)[i] | 90 (75–97) | 90 (56–99) | 92 (65–100) | 100 (65–100) |
| | 4 | 10.3 (7–15.2)[b,c,f] | 7.7 (4.2–14.3)[b,c,f] | 9.4 (4.3–20.3)[c,f] | 20.5 (11.8–35.5)[f] | 97 (86–100) | 100 (77–100) | 93 (69–100) | 100 (65–100) | 5.9 (4.0–8.9)[b,c,f] | 2.7 (1.5–4.9)[b,f,i] | 8.6 (5.1–14.4)[c,f,i] | 12.3 (5.7–26.7)[c,f,i] | 100 (90–100) | 100 (73–100) | 100 (76–100) | 100 (65–100) |

Note: Subjects qualifying for memory analyses are divided according to whether they received a pneumococcal conjugate vaccine (PCV7) or pneumococcal polysaccharide vaccine (PPV) booster dose in P1061s. Subject group refers to all subjects (all immune strata combined), immune stratum 2, immune stratum 3, and immune stratum 4, and the number of subjects in each subject group is indicated in parentheses. The subject in immune stratum 1 is included within "all subjects", but is not shown separately due to the small number of subjects in this immune stratum. ST = serotype, GMC = geometric mean concentration (mcg/mL), and CI = confidence interval.

[a] Permitted window = 6–13 days

[b] P ≤.05, antibody concentration, PCV7 recipients v. PPV recipients (Wilcoxon Rank Sum Test)

[c] P ≤.05, antibody concentration v. previous timepoint (Paired Sign Rank Test)

[d] P ≤.02, percent ≥0.5 mcg/mL v. previous timepoint (McNemar's Exact Test)

[e] Permitted window = 25–36 days, except for 1 subject whose 3rd serology was obtained at 84 days

[f] P ≤.03, antibody concentration v. week 0 (Paired Sign Rank Test)

[g] P <.01, percent ≥0.5 mcg/mL, PCV7 recipients v. PPV recipients (Fisher's Exact Test)

[h] P ≤.03, percent ≥0.5 mcg/mL v. week 0 (McNemar's Exact Test)

[i] P ≤ 0.05, antibody concentration among immune strata (Kruskal-Wallis Test)

**Table 3**

Memory responses detected in P1061s.

| ST | Pneumococcal Conjugate Vaccine 7 (PCV7) | | | | | | | | Pneumococcal Polysaccharide Vaccine (PPV) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Subject Group | | | | | | | | Subject Group | | | | | | | |
| | All (36) | 2 (14) | 3 (14) | 4 (8) | All (36) | 2 (14) | 3 (14) | 4 (8) | All (31) | 2 (10) | 3 (12) | 4 (8) | All (31) | 2 (10) | 3 (12) | 4 (8) |
| | Antibody Concentration ≥0.5 mcg/mL At Entry or Week 1, % (95% CI) | | | | ≥4-fold Rise Criterion, % (95% CI) | | | | Antibody Concentration ≥0.5 mcg/mL At Entry or Week 1, % (95% CI) | | | | ≥4-fold Rise Criterion, % (95% CI) | | | |
| 1 | 42 (26–59) | 43 (21–69) | 29 (10–58) | 63 (29–89) | 3 (0–14) | 0 (0–23) | 7 (0–31) | 0 (0–35) | 61 (43–77) | 50 (22–78) | 67 (35–88) | 75 (35–95) | 13 (5–29) | 0 (0–27) | 25 (7–55) | 13 (1–50) |
| 6B | 89 (74–96)[a] | 86 (58–97) | 86 (58–97) | 100 (65–100) | 31 (18–47)[a] | 21 (6–50) | 21 (6–50) | 63 (29–89) | 87 (71–95)[b] | 80 (44–96) | 92 (65–100) | 88 (50–99) | 13 (5–29) | 0 (0–27) | 17 (3–45) | 25 (5–65) |
| 14 | 94 (81–99)[c] | 93 (69–100) | 93 (69–100) | 100 (65–100) | 53 (35–68)[c] | 43 (21–69) | 57 (31–79) | 63 (29–89) | 94 (80–99)[d] | 90 (56–99) | 100 (76–100) | 100 (65–100) | 29 (16–47) | 20 (4–56) | 25 (7–55) | 50 (19–81) |

Note: Subjects qualifying for memory analyses are divided according to whether they received a pneumococcal conjugate vaccine (PCV7) or pneumococcal polysaccharide vaccine (PPV) booster dose in P1061s. Subject group refers to all subjects (all immune strata combined), immune stratum 2, immune stratum 3, and immune stratum 4, and the number of subjects in each subject group is indicated in parentheses. The subject in immune stratum 1 is included within "all subjects", but is not shown separately due to the small number of subjects in this immune stratum. The percentages of subjects with memory defined according to an antibody concentration ≥0.5 mcg/mL at entry or week 1 and to a ≥4-fold rise criterion (4-fold or greater antibody rise between entry and week 1) are shown. ST = serotype, CI = confidence interval.

[a] P <.01, antibody concentration ≥0.5 mcg/mL at entry or week 1 and ≥4-fold rise criterion, serotype 6B, PCV7 recipients v. serotype 1, PCV7 recipients (Fisher's Exact Test)

[b] P = .04, antibody concentration ≥0.5 mcg/mL at entry or week 1, serotype 6B, PPV recipients v. serotype 1, PPV recipients (Fisher's Exact Test)

[c] P <.0001, antibody concentration ≥0.5 mcg/mL at entry or week 1 and ≥4-fold rise criterion, serotype 14, PCV7 recipients v. serotype 1, PCV7 recipients (Fisher's Exact Test)

[d] P <.01, antibody concentration ≥0.5 mcg/mL at entry or week 1, serotype 14, PPV recipients v. serotype 1, PPV recipients (Fisher's Exact Test)

## Table 4

Predictors of immunologic memory in P1061s.

| Variable[a] | Serotype[b] | Memory Response Criterion | Odds Ratio (Confidence Interval) | P-value |
|---|---|---|---|---|
| Age | 1 | 4–fold response | .63 (.33–.96)[c] | .03 |
| | 6B | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | 78 (.61–.99)[c] | .04 |
| | 14 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | .65 (.43–.90)[c] | .01 |
| Nadir CD4% prior to HAART | 6B | 4–fold response | 1.08 (1.01–1.16)[d] | .02 |
| | 14 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | 1.14 (1.01–1.35)[d] | .04 |
| CD4% at P1024 screening | 1 | 4–fold response | 1.44 (1.13–2.20)[d] | .001 |
| | 6B | 4–fold response | 1.1 (1.02–1.20)[d] | .02 |
| CD4% at P1061s entry | 1 | 4–fold response | 1.39 (1.09–2.05)[d] | .003 |
| | 1 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | 1.08 (1.00–1.19)[d] | .04 |
| | 14 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | 1.18 (1.07–1.38)[d] | .0007 |
| CD19% at P1024 entry | 1 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | 1.39 (1.13–1.91)[d] | .0003 |
| CD19% at P1061s entry | 1 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | 1.15 (1.00–1.40)[d] | .05 |
| Logarithm P1024 viral load | 1 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | .22 (.04–.85)[e] | .03 |
| | 14 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | .21 (.04–.84)[e] | .03 |
| P1024 viral load ≤400 copies/mL (v. >400 copies/mL) | 14 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | 9.6 (1.14–202.19) | .04 |
| P1024 viral load ≤5000 copies/mL (v. >5000 copies/mL) | 1 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | 12.86 (1.69–270.89) | .01 |
| Logarithm P1061s viral load | 14 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | .30 (.09–.88)[e] | .03 |
| Logarithm P1024 antibody | 6B | 4–fold response | 3.07 (1.08–10.23)[f] | .03 |
| Concentration after PCV7-PCV7-PPV (P1024 Week 24) | 6B | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | 6.82 (1.54–42.63)[f] | .01 |
| | 14 | Antibody concentration ≥0.5 mcg/mL at entry or week 1 | 18.3 (2.18–325.15)[f] | .005 |

Note: Odds ratios and Profile Likelihood confidence intervals for variables associated with memory with a Likelihood Ratio Test P-value <0.05 in univariate analyses are shown. Memory was analyzed using 2 definitions: antibody concentration ≥0.5 mcg/mL at entry or week 1; 4-fold or greater antibody rise between entry and week 1.

[a] Other variables examined included immune stratum, time on P1061s entry HAART regimen, change in HAART due to virologic failure between P1024 and P1061s, logarithm of antibody concentration at P1024 entry, viral load ≤400 copies/mL v. >400 copies/mL at P1061s entry, viral load ≤5000 copies/mL v. >5000 copies/mL at P1061s entry.

[b] Predictors for serotype 1 are shown only for subjects who received PPV in P1061s.

[c] Odds ratio for every year increase

[d] Odds ratio for every 1% increase

[e] Odds ratio for every one logarithm (copies/mL) increase

[f] Odds ratio for every one logarithm (mcg/mL) increase