Immunogenicity and Safety of 13-Valent Pneumococcal Conjugate Vaccine in HIV-Infected Adults Previously Vaccinated With Pneumococcal Polysaccharide Vaccine


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(See the editorial commentary by Crum-Cianflone and Wallace on pages 1–4.)

Background. Persons with human immunodeficiency virus (HIV) infection are at increased risk of pneumococcal disease. We evaluated the safety and immunogenicity of 13-valent pneumococcal conjugate vaccine (PCV13) in this population.

Methods. HIV-infected persons ≥18 years of age who were previously vaccinated with ≥1 dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) and had CD4 cell counts ≥200 cells/mm³ and HIV viral loads <50 000 copies/mL were enrolled in this 3-dose PCV13 open-label study.

Results. A total of 329 subjects received ≥1 dose, and 279 received 3 doses administered at 6-month intervals. Increases in anticapsular polysaccharide immunoglobulin G concentrations and opsonophagocytic antibody titers were demonstrated 1 month after each of the 3 doses of PCV13. Antibody levels were generally similar after each dose. The responses were similar whether subjects had previously received 1 or ≥2 doses of PPSV23. Pain at the injection-site was the most common local reaction. Severe injection site or systemic events were uncommon.

Conclusions. Vaccination with PCV13 induces anticapsular immunoglobulin G and opsonophagocytic antibody responses in HIV-infected adults with prior PPSV23 vaccination and CD4 cell counts ≥200 cells/mm³. The observations support the use of PCV13 in this population.

Clinical Trials Registration. NCT00963235.

Keywords. human immunodeficiency virus; adult; pneumococcal conjugate vaccine; immunogenicity; pneumococcal polysaccharide vaccine.

As a result of humoral immune dysfunction, adults infected with human immunodeficiency virus (HIV) are at high risk for Streptococcus pneumoniae infections. The reported incidence rates of invasive pneumococcal disease in HIV-infected adults range from 197 to 5700 per 100 000 person-years, 6–324-fold higher than rates for uninfected adults [1]. Several factors may lower the rate, including use of highly active antiretroviral therapy (HAART) and introduction of pneumococcal conjugate vaccine (PCV) into the national pediatric immunization program resulting in reduced circulation of vaccine serotypes [2]. Nonetheless, based on 2 recent studies in countries where HAART is established and PCVs have been introduced, the increased risk remains approximately 20–40-fold [2, 3]. Severe and recurrent pneumococcal disease is also more common with HIV infection [1, 4, 5]. Given the increased risk for pneumococcal disease, vaccination with the 23-valent pneumococcal polysaccharide
vaccine (PPSV23) has been recommended for HIV-infected persons [6–8]. However, the magnitude and duration of responses to pneumococcal polysaccharide vaccine (PPSV) may be limited, and data on effectiveness in preventing pneumococcal disease are inconsistent [9–14]. The PCVs reduce vaccine-type invasive pneumococcal disease and radiographically confirmed pneumonia in children with HIV [15]. In addition, 7-valent PCV (PCV7) was effective against vaccine-type invasive pneumococcal disease in a randomized controlled trial of HIV-infected adults with a recent history of pneumococcal disease [16].

Immunogenicity studies with single-dose or combination regimens of PCV7 and PPSV23 have been conducted in HIV-infected adults, yielding variable results [17–28]. These data and others suggest potential benefits for the use of PCVs in persons with HIV infection [29], and 13-valent PCV (PCV13) has been added to existing recommendations for pneumococcal vaccination of immunocompromised populations [30–32].

This open-label, single-arm study is the first to describe the safety and immunogenicity of 3 doses of PCV13 given at 6-month intervals in HIV-infected adults who had previously been vaccinated with PPSV. At the time of the study, PPSV23 was recommended as part of routine care for HIV-infected persons in several countries, with the possibility of >1 vaccine administration over time [7]. Therefore, to maximize the applicability of the observations, this study recruited subjects with a history of previous PPSV23 vaccination and stratified the subjects based on receipt of either 1 or ≥2 prior doses.

METHODS

Study Design and Populations

This was a phase 3, open-label, single-arm study, in which HIV-infected adults ≥18 years of age with a documented history of vaccination with PPSV23 received 3 administrations of PCV13 at 6-month intervals. The study was conducted in the United States at 15 medical centers from November 2009 to May 2012. All subjects provided written informed consent, and human experimentation guidelines of the US Department of Health and Human Services and those of the authors’ institutions were followed in the conduct of this research. Participants were stratified (1:1) at enrollment into 2 groups, based on prior receipt of 1 or ≥2 doses of PPSV23, administered ≥6-months before the initial dose of PCV13.

At entry subjects were required to have CD4 cell counts ≥200 cells/mm³ and HIV viral loads <50 000 copies/mL, documented on the 2 most recent occasions within 6 months of the first study vaccination and were also required to be either stable for 6 weeks on HAART or not currently receiving antiretroviral therapy. Participants were excluded if they had active AIDS-related disease, including opportunistic infections or malignancy; a history of culture-proved S. pneumoniae; serious chronic disorders, including severe chronic obstructive pulmonary disease requiring supplemental oxygen, end-stage renal disease with or without dialysis, or clinically unstable cardiac disease.

Subjects attended 6 clinic visits, with 3 vaccination visits: at enrollment (dose 1) and 6 months (dose 2) and 12 months (dose 3) after enrollment, and 3 follow-up visits, 1 month (29–43 days) after each vaccination. Follow-up safety information was also collected by telephone 6 months after the third study vaccine dose.

Vaccines and Administration

PCV13 (Prevnar 13/Prevenar 13; Wyeth Vaccines) contains polysaccharides of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxin cross-reactive material 197. Each 0.5-mL dose contains 2.2 µg of each serotype, except type 6B, which is included at 4.4 µg. Each dose is formulated in 5.0 mmol/L succinate and 0.85% sodium chloride at pH 5.8 with 0.125 mg aluminum as aluminum phosphate and 0.02% polysorbate 80. The vaccine was supplied in single-dose syringes without preservatives and stored at 2°C–8°C.

Study Objectives

This study describes the safety and immunogenicity of a multiple dose series of PCV13 in HIV-infected adults who have received PPSV23. The primary immunogenicity objective was to describe the immune response after 3 administrations of PCV13 compared with the immune response after 2 administrations, each given 6 months apart, as assessed by fold rise in capsular immunoglobulin G (IgG) geometric mean concentrations (GMCs) for each vaccine serotype. Other immunogenicity objectives included description of IgG and opsonophagocytic activity antibody levels before and 1 month after each vaccination. The safety objectives were to assess local and systemic events captured in an electronic diary, as well as adverse events (AEs) and serious AEs (SAEs) after each vaccination.

Analysis Populations

The evaluable immunogenicity population was the primary population for immunogenicity analyses and comprised eligible subjects with ≥1 valid and determinate assay result, received 2 sequential doses of assigned vaccine, and had no major protocol violation. The all-available immunogenicity population comprised eligible subjects with ≥1 valid and determinate result related to the analysis. The safety population included all subjects who received ≥1 dose of PCV13 and for whom safety data were available.

Immunogenicity Assessments

Serum concentrations of anticapsular IgG for each of the 13 pneumococcal serotypes in PCV13 were determined by a validated enzyme-linked immunosorbent assay and expressed as micrograms per milliliter. The assay included a C polysaccharide–containing cell wall extract and serotype 22F capsular polysaccharide as preabsorbants [33].
Serum levels of functional antibacterial opsonophagocytic activity titers were measured using 13 serotype-specific validated assays. Opsonophagocytic activity antibody is generally accepted as a key measure of vaccine response in adults. Titers were measured as the interpolated reciprocal serum dilution that resulted in complement-mediated killing of 50% of assay bacteria. IgG concentrations and opsonophagocytic activity titers were measured in blood samples obtained before and 1 month after each vaccination.

Safety Assessments
Participants recorded local reactions (redness, swelling, and pain at injection site), systemic events (fatigue, headache, vomiting, diarrhea, new generalized muscle pain, and new generalized joint pain), and oral temperature in an electronic diary on the evening of each vaccination and for the next 13 days. Records of AEs were collected from enrollment through the 1-month follow-up visit after vaccine dose 1 and from vaccine doses 2 and 3 through their respective 1-month follow-up visits. Newly diagnosed chronic conditions and SAEs were collected through the 6-month follow-up phone contact after dose 3.

Statistical Analysis
Sample Size Estimation
The sample size for this study was based on the precision of the 2-sided 95% confidence interval (CI) for the IgG geometric mean fold rise (GMFR). A sample of 200 evaluable subjects provided precision of 0.237 on the 2-sided 95% CI for IgG mean fold rise among the 13 serotypes. Allowing for a rate of approximately 39% for dropouts and exclusions from the evaluable population due to protocol violations through the dose 3 follow-up visit, 330 enrolled subjects were expected to provide ≥200 evaluable subjects.

Enrollment was stratified by the number of previous PPSV23 doses, such that an approximately equal number were previously vaccinated with 1 dose and ≥2 doses. The precision of the 2-sided 95% CI for the IgG GMFR in each of these groups was ≥0.335.

Immunogenicity Analyses
All analyses were performed using the SAS software package (version 9.2; SAS Institute). No imputations were performed for missing data. To compute opsonophagocytic activity geometric mean titers (GMTs) and IgG GMCs, assay results were transformed to the log scale. The final statistics were reported in the original scale by back-transforming log scale data. IgG GMCs and opsonophagocytic activity GMTs were computed at each visit (before vaccination and 1 month after each vaccination). Two-sided 95% CIs were constructed at each visit by back-transforming log scale data. IgG GMCs and corresponding 2-sided 95% CIs were computed for comparison of 3 doses relative to 2 doses. Fold rises in IgG concentrations and opsonophagocytic activity titers between other defined time points were summarized by GMFRs and 2-sided 95% CIs using methods similar to that used for GMCs and GMTs. IgG GMCs, opsonophagocytic activity GMTs, IgG and opsonophagocytic activity GMFRs, ratios of GMFRs, and corresponding 2-sided 95% CIs were also generated for each stratification group.

A post hoc analysis assessed any correlation between the serotype-specific concentration of IgG or opsonophagocytic activity titer in a given subject and the time interval between the most recent PPSV23 dose and the first study vaccination.

RESULTS
Baseline Characteristics and Disposition of Subjects
A total of 329 subjects received ≥1 dose of PCV13 (mean age 47.3 years) and were included in the safety population (Table 1); 95.4% were receiving HAART and had a median CD4 cell count of 604.5 cells/mm³, with 63.8% of the population in the 51-200 cells/mm³ range. The mean time since HIV diagnosis was 13.0 years (range 1.2-28.8 years) and the mean CD4 cell count was 564 cells/mm³ (SD 237.5).

Table 1. Baseline Demographic and Clinical Characteristics
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline Value (n = 329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>79.9</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>66.6</td>
</tr>
<tr>
<td>Black/African American</td>
<td>25.2</td>
</tr>
<tr>
<td>Other</td>
<td>8.2</td>
</tr>
<tr>
<td>Hispanic or Latino, %</td>
<td>15.2</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>47.3 (19, 73)</td>
</tr>
<tr>
<td>Time since HIV diagnosis, mean (range), y</td>
<td>13.0 (1.2, 28.8)</td>
</tr>
<tr>
<td>Receiving HAART, %</td>
<td>95.4</td>
</tr>
<tr>
<td>CD4 cell count, cells/mm³</td>
<td>604.5 (237.5)</td>
</tr>
<tr>
<td>Median</td>
<td>564</td>
</tr>
<tr>
<td>HIV viral load, copies/mL</td>
<td>630.3 (3748.6)</td>
</tr>
<tr>
<td>Median</td>
<td>48.0</td>
</tr>
<tr>
<td>≤50, %</td>
<td>73.9</td>
</tr>
<tr>
<td>51 to ≤200, %</td>
<td>18.8</td>
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<tr>
<td>201 to &lt;1000, %</td>
<td>2.4</td>
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<tr>
<td>1000 to &lt;10,000, %</td>
<td>2.1</td>
</tr>
<tr>
<td>10,000 to ≤50,000, %</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; SD, standard deviation.

* Two baseline assessment were captured; the value most proximate to enrollment is presented in the table.
300 subjects (90.6%) received dose 2, and 279 (84.3%) received dose 3 (Figure 1). Two subjects consented to receive study vaccine but were not vaccinated. The majority of the safety population was white and male (66.6% and 79.9%, respectively), 25.2% were black, and 15.2% were Hispanic. The mean time since HIV diagnosis was 13.0 years, and 95% of subjects were receiving HAART at baseline. At the most recent test before the first study vaccination, 86.3% of subjects had CD4 cell counts ≥350 cells/mm³, and 73.9% had a HIV viral load ≤50 copies/mL. There were 255, 246, and 231 subjects in the evaluable immunogenicity populations for dose 1, 2, and 3, respectively. The distributions of age, race, ethnicity, and HIV status were similar in the immunogenicity analysis and safety populations.

The mean interval from the most recent PPSV23 dose to enrollment was 3.7 years (standard deviation, 2.57 years). Approximately half of the subjects (160 subjects; 48.6%), had received 1 dose of PPSV23. Of the 169 (51.4%) with a history of ≥2 doses of PPSV23, 26 had received ≥3 doses. The 2 stratification groups were generally similar in terms of age, race, and ethnicity (Supplementary Table 1). The mean duration of HIV diagnosis was slightly shorter in the group with 1 prior dose of PPSV23 compared with ≥2 doses (11.3 vs 14.7 years). Other baseline HIV-related parameters were similar between groups.

Immune Responses

IgG Responses to PCV13

Table 2 summarizes the IgG GMCs before and after each study vaccination for the evaluable population. Baseline, IgG levels were relatively low for each serotype, and an IgG response was observed after each vaccination. IgG levels after vaccinations 2 and 3 were similar to or trended slightly higher than those after vaccination 1. The IgG GMFRs (Table 2) were greatest after dose 1. Results in the all-available immunogenicity population were similar to the evaluable immunogenicity population.

The IgG levels before and 1 month after vaccination were similar between the subset of subjects who had received 1 previous dose and the subset with ≥2 previous doses of PPSV23. Moreover, there was no correlation (p values, −0.11 to 0.11) between serotype-specific IgG concentrations after study vaccination 1 and the time interval from the most recent PPSV23 dose.

Opsonophagocytic Responses to PCV13

Table 3 summarizes the opsonophagocytic activity GMTs for the evaluable immunogenicity population before and after each vaccination. The GMTs 1 month after vaccine dose 1 were higher than before dose 1 and similar or modestly higher after doses 2 and 3. Opsonophagocytic activity levels decreased between doses, but remained above baseline levels. Similar to the IgG responses, the GMFRs were greatest after the first
Table 2. IgG GMC at Each Time Point and GMFR Between Select Time Points

<table>
<thead>
<tr>
<th>Serum Type</th>
<th>Before Dose 1</th>
<th>After Dose 1</th>
<th>Before Dose 2</th>
<th>After Dose 2</th>
<th>Before Dose 3</th>
<th>After Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.56</td>
<td>2.12</td>
<td>1.27</td>
<td>2.36</td>
<td>1.24</td>
<td>2.15</td>
</tr>
<tr>
<td>3</td>
<td>0.20</td>
<td>0.49</td>
<td>0.30</td>
<td>0.57</td>
<td>0.31</td>
<td>0.55</td>
</tr>
<tr>
<td>4</td>
<td>0.26</td>
<td>1.42</td>
<td>0.76</td>
<td>1.64</td>
<td>0.84</td>
<td>1.66</td>
</tr>
<tr>
<td>5</td>
<td>1.81</td>
<td>2.99</td>
<td>2.43</td>
<td>3.28</td>
<td>2.51</td>
<td>3.26</td>
</tr>
<tr>
<td>6A</td>
<td>0.97</td>
<td>2.97</td>
<td>2.01</td>
<td>3.85</td>
<td>2.42</td>
<td>4.60</td>
</tr>
<tr>
<td>6B</td>
<td>1.17</td>
<td>3.06</td>
<td>2.12</td>
<td>4.48</td>
<td>2.63</td>
<td>5.48</td>
</tr>
<tr>
<td>7F</td>
<td>0.87</td>
<td>3.39</td>
<td>2.19</td>
<td>3.39</td>
<td>2.16</td>
<td>3.60</td>
</tr>
<tr>
<td>9V</td>
<td>0.92</td>
<td>2.63</td>
<td>1.88</td>
<td>2.96</td>
<td>2.00</td>
<td>3.18</td>
</tr>
<tr>
<td>14</td>
<td>2.40</td>
<td>6.29</td>
<td>5.22</td>
<td>7.62</td>
<td>5.50</td>
<td>8.13</td>
</tr>
<tr>
<td>18C</td>
<td>0.69</td>
<td>2.90</td>
<td>1.86</td>
<td>2.72</td>
<td>1.92</td>
<td>3.05</td>
</tr>
<tr>
<td>19A</td>
<td>2.69</td>
<td>6.53</td>
<td>4.82</td>
<td>7.57</td>
<td>5.19</td>
<td>7.81</td>
</tr>
<tr>
<td>19F</td>
<td>0.72</td>
<td>2.71</td>
<td>1.99</td>
<td>5.63</td>
<td>3.14</td>
<td>6.48</td>
</tr>
<tr>
<td>23F</td>
<td>0.81</td>
<td>2.70</td>
<td>1.66</td>
<td>3.74</td>
<td>2.25</td>
<td>4.76</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; GMFR, geometric mean fold rise; IgG, immunoglobulin G.

Table 3. Opsonophagocytic Activity GMT at Each Time Point and GMFRs Between Select Time Points

<table>
<thead>
<tr>
<th>Serum Type</th>
<th>Before Dose 1</th>
<th>After Dose 1</th>
<th>Before Dose 2</th>
<th>After Dose 2</th>
<th>Before Dose 3</th>
<th>After Dose 3</th>
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<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>38</td>
<td>15</td>
<td>40</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>28</td>
<td>11</td>
<td>43</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>631</td>
<td>210</td>
<td>701</td>
<td>230</td>
<td>743</td>
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<tr>
<td>5</td>
<td>7</td>
<td>63</td>
<td>24</td>
<td>63</td>
<td>25</td>
<td>71</td>
</tr>
<tr>
<td>6A</td>
<td>17</td>
<td>952</td>
<td>354</td>
<td>1704</td>
<td>592</td>
<td>2117</td>
</tr>
<tr>
<td>6B</td>
<td>83</td>
<td>1050</td>
<td>473</td>
<td>1807</td>
<td>719</td>
<td>2388</td>
</tr>
<tr>
<td>7F</td>
<td>42</td>
<td>769</td>
<td>328</td>
<td>939</td>
<td>384</td>
<td>1062</td>
</tr>
<tr>
<td>9V</td>
<td>35</td>
<td>416</td>
<td>201</td>
<td>693</td>
<td>189</td>
<td>880</td>
</tr>
<tr>
<td>14</td>
<td>197</td>
<td>651</td>
<td>397</td>
<td>700</td>
<td>480</td>
<td>812</td>
</tr>
<tr>
<td>18C</td>
<td>33</td>
<td>453</td>
<td>171</td>
<td>541</td>
<td>199</td>
<td>705</td>
</tr>
<tr>
<td>19A</td>
<td>34</td>
<td>282</td>
<td>145</td>
<td>387</td>
<td>176</td>
<td>415</td>
</tr>
<tr>
<td>19F</td>
<td>13</td>
<td>123</td>
<td>53</td>
<td>253</td>
<td>66</td>
<td>242</td>
</tr>
<tr>
<td>23F</td>
<td>8</td>
<td>93</td>
<td>33</td>
<td>281</td>
<td>77</td>
<td>400</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GMT, geometric mean titer; OPA, opsonophagocytic activity.

Oxponophagocytic activity GMTs in subjects with 1 previous dose of PPSV23 were similar to those with ≥2 previous doses, shown for each dose over time in Figure 2 and by select
time points in Supplementary Figure 1. As with the IgG results, there was no correlation ($\rho$ values, $-0.04$ to $0.20$) between the serotype-specific opsonophagocytic activity titers after dose 1 and the time interval from the most recent PPSV23 dose.

**Safety**

Table 4 summarizes the prompted local reactions and systemic events occurring through 14 days after each vaccination. In general, the percentages of subjects with local reactions did not consistently increase over the 3 doses. The majority of local reactions were mild. Pain was the most frequently occurring local reaction after each vaccination. The percentage of subjects with severe pain was higher after vaccine doses 2 (8.1%) and 3 (5.7%) than after dose 1 (1.3%). After vaccination 3, the percentages of subjects with any redness and any swelling were slightly higher in subjects with $\geq 2$ previous doses of PPSV23 (12.3% and 13.6%, respectively) than in those with 1 previous dose (6.3% and 8.3%, respectively). The rates of severe redness or severe swelling were similar between groups.

The most frequent prompted systemic events after each vaccination were fatigue, headache and new generalized muscle pain. The percentage of subjects with fever $\geq 38.0^\circ\text{C}$ was low after vaccinations 1, 2, and 3 (6.2%, 5.1%, and 7.7%, respectively). After dose 3, fatigue, headache, and vomiting rates trended slightly higher in subjects with $\geq 2$ previous doses of PPSV23 than in those with 1 previous dose (48.5%, 40.0%, and 6.3%, respectively).

AEs were reported after any dose by 63.5% of subjects, with the most frequent being upper respiratory tract infection (7.0%), fatigue (4.0%), diarrhea (3.3%), bronchitis (3.3%), and rash (3.3%). There were no deaths and no vaccine-related SAEs.

**DISCUSSION**

The PCVs use capsular polysaccharides conjugated to immunogenic proteins to induce serotype-specific T-cell dependent responses. Conjugate vaccines induce amnestic responses, which may lead to increased duration of effect and a booster response [38]. Both PCV7 and a related 9-valent vaccine induce...
responses with specificity and functional activity and are protective in HIV-infected populations, including a study in Malawi in which a 2-dose series of PCV7, given 4 weeks apart, reduced vaccine-type invasive pneumococcal disease in HIV-infected adults with a recent history of pneumococcal disease [15, 16, 19, 21]. PCV13, containing 13 different conjugates, expands serotype coverage and has been evaluated in healthy infants, children, and adults [39].

The present study assessed the safety and immunogenicity of PCV13 given in 3 doses to HIV-infected adults. The study population comprised HIV-infected adults previously vaccinated with ≥1 dose of PPSV23. Certain findings in healthy older adults and HIV-infected adults suggest that prior PPSV23 may result in lower responses to subsequent pneumococcal vaccine [40–42]. Given the potential risks factors for impaired response (HIV infection, previous PPSV), the study population was considered a group that might benefit from a series of PCV13 doses as opposed to a single dose. A relatively prolonged interval of 6 months between PCV13 doses was selected to explore the potential for enhanced immunogenicity [43].

This study demonstrated that a dose of PCV13 elicited both pneumococcal anticapsular polysaccharide IgG and opsonophagocytic antibodies to all vaccine serotypes in HIV-infected adults with prior PPSV, and was evaluated in healthy infants, children, and adults [39].

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safety findings after 1, 2, and 3 doses of PCV13 in this study are similar to those described after a single PCV13 or PPSV23 vaccination in HIV-uninfected adults [36].

The findings of this study were consistent with those in studies of PCV7 in HIV-infected adults that demonstrate a functional antibody response after vaccination [18–20, 27, 29]. The impact of 1 versus 2 doses of PCV7 in HIV-infected adults has been evaluated as well, but studies have reached somewhat disparate conclusions [19, 24, 41]. Comparisons between these relatively small studies should be interpreted cautiously, because they vary by PPSV vaccination status, immune status (CD4 cell counts and HIV viral loads), use of HAART, number of serotypes tested, and criteria for a response. In a small US study of HIV-infected adults naive to pneumococcal vaccine, Feikin et al [19] found no enhancement and slight diminution of IgG and opsonophagocytic responses to the subset of serotypes measured after a second dose of PCV7 given 4 weeks after an initial dose. However, in a study of HIV-infected Ugandan adults by Miiro et al [24], some of whom had previously received PPSV23, a second dose of PCV7, given 4 weeks after the first, elicited higher IgG GMCs for serotypes 4, 6B, 19F, and 23F. A nonrandomized trial in Taiwan by Lu et al [41] also found that administering a second dose of PCV7 8 weeks after the first dose to HIV-infected adults who had received PPSV >5 years earlier resulted in a higher rate of IgG responses to ≥2 serotypes of 4 serotypes measured.

In the current study, no diminution of responses was associated with a second or third dose of PCV13 administered at 6-month intervals. Each vaccination induced a functional immune response, and for certain serotypes the opsonophagocytic activity GMT was modestly higher with subsequent doses. However, the increases were incremental, and even after the third vaccination, titers were lower than after a single dose of PCV13 in PPSV–naïve healthy adults ≥50 years of age, although higher than in 70-year-old adults preimmunized with polysaccharide vaccine [36, 37, 42]. Therefore, our study suggests a limited impact of additional doses given at an interval of 6 months after a single dose of PCV13 in HIV-infected adults. Longer-term guidance for additional doses of pneumococcal vaccine over the course of many years in chronically immunocompromised populations awaits further study.

Our study has several limitations. There was no PPSV23 control in this study, because the purpose was not comparison with PPSV. Moreover, data from studies in older healthy and HIV-infected adult populations have suggested that subsequent doses of PPSV after an initial dose may result in reduced responses; therefore, inclusion of such a treatment arm was not considered sufficiently compelling [37, 40, 44]. This study also did not include a pneumococcal vaccine–naïve control group, because PPSV23 was recommended for HIV-infected individuals in the study setting, limiting the potential pool of unvaccinated persons for enrollment. Of note, in the current study there was no substantial difference in response between the groups with a past history of 1 dose versus ≥2 doses of PPSV23. Finally, in this study, as with other studies using immunogenicity endpoints, clinical outcomes may only be inferred and were not directly assessed.

Based on the potential benefit, several countries recommend a dose of PCV13 for HIV-infected adults, including those previously vaccinated with PPSV23 [30, 31]. A significant number of HIV-infected adults have already received PPSV23, and the findings of safety and immunogenicity from the current study support the use of PCV13 in this population.

### Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

### Notes

**Acknowledgments.** We would like to thank the other investigators of the 6115A1-3017 study group: Judith Aberg, Thomas Campbell, Alan Cohen, Richard Elion, Jonathan Moorman, Marica Sokol-Anderson, Louis Sloan, Francis Wallach, Amneris Luque, and Michael Yin. We also thank James Trammel and the programming staff at Inventiv for support with data analysis.

**Financial support.** This work was supported by Wyeth Vaccines Research, which was acquired by Pfizer Inc in October 2009. The sponsor and all authors were involved in the study design, data collection, and/or interpretation of data, writing of the manuscript, and the decision to submit the manuscript for publication.

**Potential conflicts of interest.** W. W., R. N., A. G., D. A. S., E. A. E., W. C. G., and B. S.-T. are current employees of Pfizer and may hold stock options. V. S. is a current employee of Inventiv, contracted by Pfizer for work on this study. M. J. G., C. B., R. N. G., J. P. L., and D. S. received funding to their institutions from Pfizer to conduct this study. M. J. G. served as a consultant to Pfizer as a member of the steering committee of this trial. The University of Kentucky (R. N. G.) has received research grants from ViroPharma, T2, PaxVax, and Bavarian-Nordic.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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