Stimulating Evidence for Pneumococcal Conjugate Vaccination Among HIV-Infected Adults

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(See the major article by Glesby et al on pages 18–27.)

Keywords. Streptococcus pneumoniae; pneumococcal; HIV-infected persons; vaccines; conjugate vaccine.

Streptococcus pneumoniae remains a formidable foe—it is the leading cause of bacterial pneumonia and an important cause of invasive disease. Adults infected with human immunodeficiency virus (HIV) are at particular risk for invasive pneumococcal disease (IPD), with an approximate 40-fold risk compared with the general population despite the advent of combination antiretroviral therapy (cART) [1–3]. Furthermore, up to 25% of HIV-infected persons develop recurrent disease, most commonly because of reinfection [4, 5]. The annual IPD incidence of 245 cases per 100 000 among HIV-positive adults in the developed world [2] points to the need for additional modalities to prevent this all too common infection.

The burden of pneumococcal disease among adults infected with HIV may be mitigated by several strategies including the use of effective cART, the avoidance of specific modifiable behaviors (eg, smoking, illicit drug use), prophylaxis against Pneumocystis carinii pneumonia (ie, trimethoprim-sulfamethoxazole), and annual influenza vaccination [1, 6, 7]. The most specific intervention to reduce IPD is the use of pneumococcal vaccination [6]. Two types of pneumococcal vaccines currently exist—a pneumococcal polysaccharide vaccine containing 23 serotypes (PPSV23) available since 1983, and pneumococcal conjugate vaccines (PCVs), available since 2000 as a 7-valent (PCV7) and since 2010 as a 13-valent (PCV13) formulation.

Given the risk of IPD among HIV-infected persons, vaccine advisory committees have recommended pneumococcal vaccinations since the 1980s [8]. Initially, guidelines advised a single dose of PPSV23 at HIV diagnosis, followed by revaccination at 5 years and then again at age 65 years (assuming ≥5 years had elapsed since last vaccine). Unfortunately, after PPSV23 anti-pneumococcal antibody levels rapidly decline [9], leaving HIV-infected patients at continued substantial risk for IPD [10–12].

More recent guidelines [6, 13–15] have added PCV to the list of recommended vaccines. The recommendation for the use of PCV among HIV-infected adults was supported by data showing that PCV elicits superior immunologic responses [16–21] and convincing results from a randomized, double-blind, placebo-controlled trial of PCV (using the PCV7) among HIV-infected adults in Malawi [22]. The Malawi study found that PCV7 had a 74% efficacy against vaccine-type IPD among HIV-infected adults with a prior history of IPD, with demonstrable efficacy even among those with low CD4 cell counts (<200 cells/mm³). Because PCV is an excellent priming vaccine, it is preferably administered as the first pneumococcal vaccine [18, 19, 23], and current guidelines recommend administration of PCV at HIV diagnosis, followed by PPSV23 ≥8 weeks later [6, 13–15]; PPSV23 continues to be recommended given the limited serotype coverage of the currently available conjugate vaccine.

Although this may be the ideal sequencing for pneumococcal vaccinations, many HIV-infected adults in care have already received ≥1 dose of PPSV23. Guidelines have suggested that, in this situation, a single dose of PCV13 should be administered ≥1 year after the last PPSV23 [6, 13–15]. However, in immunogenicity studies to date, the value of PCV7 after an initial PPSV23 dose has been mixed [16, 24].

In this issue of the Journal, Glesby et al [25] report a large (n = 329) study of the immunogenicity and safety of PCV13 administered as 3 sequential doses at 6-month intervals. The study population consisted of HIV-infected adults who had previously received ≥1 dose of PPSV23 and had a CD4 cell count ≥200 cells/mm³ and an HIV RNA level <50 000 copies/mL. Approximately 95% of study
participants were receiving cART. The study’s main finding was that PCV13 stimulated pneumococcal capsular polysaccharide immunoglobulin (Ig) G and opsonophagocytic antibodies to all PCV13 serotypes. This study is unique in that it evaluated the immunogenicity of PCV13 in HIV-infected adults, whereas prior studies investigated PCV7.

The study by Glesby et al [25] is of particular importance, because other studies have suggested that PPSV23 may attenuate responses to subsequent pneumococcal vaccination, including PCV [26, 27]. Because of this concern, Glesby et al examined additional doses of PCV13 (up to 3 doses over time) and found that despite prior PPSV23, PCV13 elicited IgG immune responses and complement-mediated killing against pneumococci after each PCV13 dose. Another concern has been that HIV-infected patients who have received multiple PPSV23 doses may not benefit from subsequent PCV administration. Again, Glesby et al provide important data that immune responses to PCV13 vaccination did not seem to be influenced by the number of prior PPSV23 vaccinations. Of note, most participants in the study had received 1 or 2 prior doses of PPSV23; a few (n = 26; 8% of the study population) had received ≥3 doses.

Similar to findings in the general population, there were no concerning safety signals with PCV13 vaccination among HIV-infected patients in the current study [25]. The most common adverse event was local pain at the injection site. Although injection site pain seemed more prominent after the second and third PCV13 doses, there was no significant trend over time, and rates of more serious events, such as fever, were similar with sequential PCV13 doses.

Although the study by Glesby et al [25] provides immunogenicity data after the receipt of PCV13 vaccinations among HIV-infected adults, it does not provide information about the optimal number of PCV13 vaccinations for HIV-infected adults. Current recommendations suggest that a single dose of PCV13 should be administered to HIV-infected adults. Although 3 sequential PCV13 doses were administered at 6-month intervals, the value added by the second and third vaccinations was not established by the study’s results [25], which demonstrated only small geometric mean fold rises in antibody levels after each subsequent dose. Hence, the study’s specific dosing schedule (PCV13 every 6 months for 3 doses) cannot currently be recommended.

Whether HIV-infected patients would benefit from additional PCV13 doses, perhaps given at longer intervals, remains an important question. Although the current study [25] did not have an HIV-negative control arm, prior studies with such groups have shown that HIV-infected patients’ postvaccine immune responses are substantially less robust [23, 24], suggesting the potential need for enhanced vaccine strategies. Data on the long-term durability of IgG and opsonophagocytic antibodies levels over time among HIV patients may be informative, although, to our knowledge, there are no current immunologic correlates of clinical protection against IPD among adults. To date, the only study among HIV-infected adults that has examined clinical outcomes after PCV [22] found that efficacy was highest during the first year after vaccination and seemed to diminish thereafter (from 85% to 25%), although the absolute numbers after year 1 were quite small.

Additional studies will be needed to determine the potential value of additional PCV13 vaccinations beyond the single dose recommended by the current guidelines [6, 13–15]. Ultimately, the potential use of PCV as a multidose vaccine may vary based on whether it is used as the initial pneumococcal vaccine or revaccination [17, 22], and by host characteristics, such as immunocompetence and receipt of cART at the time of vaccination [28].

Another important consideration is the timing of pneumococcal vaccinations. The current study [25] does not define the optimal timing for additional pneumococcal doses. However, the study found no correlation between vaccine immune responses and the time interval between PPSV23 and the first PCV13 dose; of note, vaccine administrations in the study were a median of 3.7 years apart and required separation by ≥6 months. Until further data are available, current vaccine guidelines [13] recommend that PCV13 be given ≥1 year after receipt of PPSV23.

Limitations of the current study [25] include the fact that the generalizability of the findings may be limited to the study participant characteristics. The study does not provide data among HIV-infected patients from diverse international populations, who may differ by genetic, nutritional, and immune backgrounds and may have varying responses to pneumococcal vaccinations [29]. In addition, the study did not evaluate those with high-level immunocompromise (CD4 cell counts <200 cells/mm3) or with poorly controlled disease (HIV RNA ≥50 000 copies/mL and/or active AIDS-related conditions). Data among these groups are imperative, given that they historically have the poorest vaccine immune responses and yet are at greatest risk of IPD [11].

Although the clinical impact of the addition of PCV13 among HIV-infected adults is unclear, it is likely that this vaccine will provide an additional layer of protection against IPD. Compared with polysaccharide vaccines, PCVs elicit greater initial and amnestic immune responses [19]. Furthermore, 39%–61% of IPD cases among HIV-infected adults are caused by serotypes included in PCV13 [2, 30], providing an additional rationale for using PCV13 in this population.

The study by Glesby et al [25] contributes to the growing supportive data on the use of PCV13 among a variety of at-risk populations, including HIV-infected adults. However, much work remains to be done to protect this vulnerable population. Future studies should examine the optimal timing and number of PCV doses among HIV-infected patients. Studies must also include those at greatest risk...
The content of the manuscript have been disclosed. for Disclosure of Potential Con-
sole responsibility of the authors.
ent and views expressed in this publication is the
decision to submit it for publication. The con-
content of the manuscript and concurred with
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ly vaccinated with PPSV23. These data
high-quality evidence that PCV13 stimu-
valency and strategies to enhance vaccine
infectious disease among HIV-
Notes
Potential conflict of interest. Both authors: No reported conflicts.
Disclaimer. Both authors contributed to the content of the manuscript and concurred with
the decision to submit it for publication. The con-
tent and views expressed in this publication is the sole responsibility of the authors.
Both 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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