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Pneumococcal vaccination among HIV-infected adult patients in the era of combination antiretroviral therapy

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Abbreviations: ACIP, Advisory Committee on Immunization Practices; ART, antiretroviral therapy; cART, combination antiretroviral therapy; DHHS, Department of Health and Human Services; EACS, European AIDS Clinical Society; ELISA, enzyme-linked immunosorbent assay; GMT, geometric mean titer; IPD, invasive pneumococcal disease; NA, not available; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; PVL, plasma HIV RNA load; TLR, toll-like receptor

HIV-infected patients remain at higher risk for pneumococcal disease than the general population despite immune reconstitution and suppression of HIV replication with combination antiretroviral therapy. Vaccination with 23-valent pneumococcal polysaccharide vaccine (PPV23) composed of T-cell-independent antigens has been recommended to reduce the risk of pneumococcal disease in HIV-infected adults. However, given the heterogeneity of study design, execution and subjects enrolled, studies examining serological responses to PPV23 yielded conflicting results and observational studies of clinical effectiveness only provided moderate evidence to support the routine use of PPV23 in HIV-infected adults. Pneumococcal conjugate vaccine (PCV), with conjugation of the capsular polysaccharide to a protein carrier, is more immunogenic than PPV23 and has been demonstrated to protect against pneumococcal disease in HIV-infected children and recurrent invasive pneumococcal disease in HIV-infected adolescents and adults. Guidelines have recently been revised to recommend that HIV-infected patients aged 19 y or older receive one dose of 13-valent pneumococcal conjugate vaccine (PCV13) followed by a booster vaccination with PPV23. In this paper, we review the studies using different vaccination strategies to improve immunogenicity among HIV-infected adult patients.

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Introduction

HIV infection results in defects in cell-mediated immunity, B cell dysfunction, loss of memory B cell subset, and suboptimal humoral immune responses,[1-7]which increase the vulnerability of HIV-infected patients to acquire *Streptococcus pneumoniae* infection. In addition, older age, coinfection with hepatitis viruses, co-morbidities, cigarette smoking, and substance abuse are also associated with an increased risk of pneumococcal pneumonia and/or invasive pneumococcal disease (IPD), defined as isolation of *S. pneumoniae* from a normally sterile site such as blood, cerebrospinal fluid or pleural fluid, while antiretroviral therapy, influenza vaccination and antibiotic prophylaxis are associated with a decreased risk.[8]

Without effective antiretroviral therapy, HIV-infected patients may have more than 100 times higher risk for IPD than age-matched populations, with high recurrence rates (8–25%).[9] For example, in San Francisco, the estimated rate of pneumococcal bacteremia in AIDS patients at the beginning of the HIV epidemic was 9.4 cases per 100 person-years, which was much higher than that in the general population before the HIV epidemic (0.075–0.164 cases per 100 person-years).[10-12] Of note, pneumococcal pneumonia and IPD can occur early in the course of HIV infection, before onset of other opportunistic infections specifically associated with AIDS.[13-15]

With the introduction of zidovudine monotherapy or dual antiretroviral therapy, the risk of pneumococcal disease as well as other AIDS-related morbidity and mortality decreased in HIV-infected patients; however the clinical benefit was not durable

because of emergence of HIV-1 with resistance to therapy containing only one or 2 antiretroviral agents.[16,17] The advent of combination antiretroviral therapy (cART) in the mid-1990s has further led to significant decline in the incidence of pneumococcal disease among HIV-infected patients with access to cART in developed countries.[18-20] Heffernan et al have shown that the annual incidence of IPD in the United States declined from 10.9 cases per 1000 persons (July 1995–June 1996, pre-cART era) to 4.7 cases per 1000 persons (July 1999–June 2000, post-cART era) in HIV-infected patients with AIDS[18]; and Saindou et al reported that the incidence of community-acquired pneumococcal pneumonia in France declined from 10.6 cases per 1000 person-years in HIV-infected patients enrolled in the pre-cART era to 2.5 cases per 1000 person-years in those in the post-cART era.[19] Despite cART, the risk of pneumococcal disease remains elevated for HIV-infected persons compared with HIV-uninfected persons (10–60-fold).[19,21-25] Although these studies were mainly conducted in the early cART era consisting of HIV-infected patients with CD4 cell counts <200 cells/μl, a recent study in the UK, in which more than 80% of HIV-infected adults with a CD4 cell count <350 cells/μl were receiving cART, still reported a 20-time higher risk of IPD among HIV-infected adults compared to the general population.[25] Therefore, other preventive interventions for pneumococcal disease are necessary among HIV-infected patients.

To prevent pneumococcal disease among HIV-infected patients, vaccination with a single dose of 23-valent pneumococcal polysaccharide vaccine (PPV23) to all HIV-infected adults regardless of their CD4 cell counts has been recommended since the first version of guidelines on prevention of HIV-related opportunistic infections by the US. Public Health Service and the Infectious Diseases Society of America in 1995.[26-30] Revaccination with PPV23 was also recommended in the newer versions of guidelines for those persons who have initial CD4 lymphocyte counts of <200 cells/μL at primary vaccination and whose CD4 counts increase to 200 cells/μL or greater with cART,[29,30] and for those whose vaccination occurs 5 y earlier.[30] However, 23-valent PPV that is composed of T-cell-independent antigens is known to be a poor inducer of immunologic memory. In the only randomized clinical trial of PPV23 in HIV-infected Ugandan adults, vaccination with PPV23 did not confer benefit in terms of preventing IPD, pneumococcal disease or overall mortality; in contrast, patients receiving PPV23 had a 60% higher risk of all-cause pneumonia than those receiving placebo.[31] A recent systematic review by Pedersen et al[8] included the aforementioned randomized trial[31] and 15 observational studies to assess the clinical effectiveness of PPV23 in preventing pneumococcal disease or IPD. Two of 7 studies that investigated the effectiveness of PPV23 in preventing pneumococcal disease and 5 other studies that investigated the effectiveness in preventing IPD found no significant protective effect. Despite the limitations by the heterogeneity of study design and execution of these observational studies, the authors concluded that currently available evidence is only moderate to support the routine use of PPV23 in HIV-infected patients and newer or more immunogenic vaccines are needed.[8]

With respect to immunogenicity of PPV23, the results of published studies are summarized in **Table 1**,[31-41] which are much more difficult to interpret than the clinical effectiveness studies because of differences in study design, comparators enrolled, CD4 counts and receipt of antiretroviral therapy, especially cART, of the subjects, pneumococcal serotypes assessed, timing of blood sampling, follow-up duration, methods to assess the response (enzyme-linked immunosorbent assay [ELISA] or opsonophagocytic activity [OPA] assay), definitions used for immune response (fold rise of antibody, antibody concentration, or geometric mean concentration or titer). Despite the renumeration of CD4 counts with cART, several studies have shown that most patients failed to maintain durable antibody response for most serotypes following vaccination with PPV23 over the 5-year follow-up period, especially those who had low CD4 counts at vaccination and uncontrolled HIV replication.[38,42,43] Moreover, in HIV-infected patients receiving long-term cART who had received primary vaccination with PPV23 5 y earlier, revaccination with PPV23 elicited significantly poorer antibody responses than revaccination with one or 2 doses of 7-valent pneumococcal conjugate vaccines (PCV7).[41]

Pneumococcal conjugate vaccines (PCVs), wherein conjugation of the capsular polysaccharide to a protein carrier converts the polysaccharide into a T cell-dependent antigen, have been shown to protect against IPD in HIV-infected children[44] and recurrent IPD in HIV-infected Malawian adolescents and adults.[45] However, how to maximize the effectiveness of PCV in the HIV-infected adults remains controversial. In this article we review the immunogenicity studies of the PCVs in HIV-infected patients in the cART era.

Guidelines of Vaccination with PCVs for HIV-infected Adults in the cART Era

In 2012, the Advisory Committee on Immunization Practices (ACIP) of Centers for Disease Control and Prevention and updated DHHS Guidelines recommend that all HIV-infected patients aged 19 y or greater, regardless of CD4 counts, receive pneumococcal vaccination.[46,47] Individuals who are pneumococcal vaccine-naïve should receive one dose of PCV13 first. Patients with CD4 counts ≥200 cells/μL should be given one dose of PPV23 at least 8 weeks after receiving PCV13. For patients with CD4 counts <200 cells/μL, PPV23 could be offered 8 weeks after receiving PCV13, or deferred until the CD4 counts increase to >200 cells/μL with cART. For individuals who have already received PPV23, one dose of PCV13 should be given at least one year after the most recent dose of PPV23. Subsequent revaccination with PPV23 is recommended for individuals of 19–64 y if more than 5 y have elapsed since the first dose of PPV23 with no more than 3 lifetime doses. Once the patient is older than 65 y, another dose of PPV23 should be given if 5 y have elapsed since the previous PPV23 dose. Similarly, the European AIDS Clinical Society (EACS) Guidelines also recommended providing PCV13 instead of PPV23 to HIV-infected adults if available since 2013.[48] In the 2012 WHO position paper of pneumococcal

Table 1. Immunogenicity studies assessing the antibody responses to 23-valent pneumococcal polysaccharide vaccine (PPV23)

Reference	Study period	Design	Comparators (n=)	CD4 count, cells/μl; <200 cells/μl, %	PVL, log_{10} copies/ml	ART or cART	Methods (serotypes assessed)	Sampling time	Definition of antibody response	Immunogenicity
31	1995–1998	Randomized	PPV23 (667) vs placebo (656)	43% vs 45%	NA	NA	ELISA (8)	Mo 1	2-fold rise	41% vs NA
32	NA	Cohort	CD4 >300 (20) vs <300 cells/μl (40)	0% vs NA	NA	NA vs 50% (ART)	ELISA (3, 4) OPA (3)	Wk 1, 2, 4, 12	2-fold rise	94% vs 68%
33	Jul-Dec 1993	Randomized	PCV (141) vs PPV23 (141)	32% vs 32%	NA	51% vs 44% (ART)	ELISA (6B, 14, 18C, 19F, 23F)	Mo 1	GMT; 2-fold rise	5–66% vs 24–71%
34	NA	Cohort	No IPD (33) vs IPD (21)	*330 (37) vs 189 (37)	NA	NA	ELISA (1, 6B, 14, 19F)	Mo 1	Fold rise, killing activity	2.0–7.0 vs 2.0–4.2
35	1991–1994	Cohort	CD4 <200 (26) vs >200 cells/μl (24)	48 vs 427	NA	NA	ELISA (14, 18C, 19F, 23F)	Yr 5	Mean rate of decline of GMC (SD)	0.014 (0.01) vs 0.014 (0.002) μg/ml per month
36	2002–2003	Randomized	PCV7/PPV23 (106) vs PPV23 (106)	*351 (72) vs 350 (75)	NA	88% vs 86% (ART)	ELISA (4, 6B, 9V, 14, 18C, 19F, 23F)	Wk 0, 4, 8, 24	2-fold rise and IgG ≧1 μg/ml	17–30% vs 10–40% at wk24
37	2001–2004	Cohort	cART (89) vs no cART (24)	NA	NA	100% vs 0%	ELISA (1, 6B, 14, 19F, 23F)	At baseline, mo 12	Mean-fold rise between baseline and mo 12	1.4–3.8
38	NA	Cohort	CD4 <100 (35) vs 100–199 (36) vs 200–349 (34) vs >350 cells/μl (64)	#45 vs 146 vs 263 vs 457 at vaccination	49% vs 67% vs 82% vs 78% (<400 copies/mL)	NA	ELISA (6B, 14, 19F, 23F)	Annually for 5 Yr	2-fold rise or ≧ 0.35 μg/ml	Responses to PPV declined significantly over the 5-Yr follow-up
39	NA	Cohort	cART-naive (20) vs cART-treated (75)	#493 vs. 649	#4.33 vs 1.60	NA	ELISA (4, 6B, 9V, 14, 18C, 19F, 23F); OPA (6B, 14, 19F, 23F)	Mo 9	2-fold rise to 1 μg/ml for at least 5 serotypes	IgG loss greater in cART-naïve; OPA higher in patients on cART
40	2004–2007	Randomized	Immediate (PCV, PPV23) (42) vs. delayed (PCV, PPV23) (37)	#60 (overall)	#5.02 (overall)	NA	ELISA (4, 6B, 9V, 14, 18C, 19F); OPA (14, 18C, 19F, 23F)	Mo 6 and 12	2-fold rise in IgG concentration; OPA titer of >2	No difference between 2 PCV and PPV23; higher responses in delayed arm
41	2005–2010	Cohort	PPV23/PCV7–1 (50) vs PPV23/PCV7–2 (44) vs PPV23/PPV23 (127)	0% vs 9.1% vs 7.8%	82.0% vs 84.1% vs 82.0% vs 82.7% (<1 .6)	90% vs 90.9% vs 100%	ELISA (6B, 14, 23F, 19F)	Wk 48 post re-vaccination	2-fold rise and IgG ≧1 μg/ml	32.0% vs 63.6% vs 8.7%

Note: *mean (standard deviation) for CD4 count (cells/μL); #median

Abbreviations: ART, antiretroviral therapy; GMT, geometric mean titer; cART, combination antiretroviral therapy; NA, not available; PCV, pneumococcal conjugate vaccine; PVL, plasma HIV RNA load;

vaccines, routine vaccination with PPV23 among HIV-infected adults in resource-limited countries was no longer recommended because of the low level of evidence for benefit. The inclusion of PCVs in childhood immunization programs worldwide is recommended, and PCVs are considered safe in all target groups for vaccination, including in immunocompromised individuals. However, whether PCVs should be routinely recommended to all HIV-infected adults remained unanswered.[49] On the other hand, the British national guidelines by the Public Health England, which has been updated in 2013, still recommends one dose of PPV23 for HIV-infected adults [50].

Clinical Efficacy of PCV in HIV-infected Adults

In the only clinical efficacy trial of PCV7 in the adults and adolescents, French et al enrolled 496 Malawians aged 15 y or greater, 437 (88%) being HIV-infected, who had recovered from IPD to receive 2 doses of PCV7 or placebo administered 4 weeks apart. The primary outcome of interest was recurrent episodes of IPD caused by vaccine serotypes or serotype 6A.[45] After a median follow-up of 1.2 y, 67 episodes of IPD occurred in 52 HIV-infected patients. Episodes of IPD were most common in the subgroup of participants with CD4 count <200 cells/μl at baseline. The vaccine efficacy was 74% (95% confidence interval, 30 to 90) in HIV-infected patients, which decreased from 85% in the first year post-vaccination to 25% thereafter. In multivariate analysis, patients with a CD4 count <200 cells/μl at baseline had 7.1-fold greater risk for developing recurrent IPD than those with a CD4 count >500 cells/μl.

In this study, *S. pneumoniae* of vaccine serotypes and serotype 6A accounted for only 50% of the episodes of IPD in the placebo group; furthermore, only 13% of HIV-infected participants were receiving cART at baseline. Therefore, PCVs with broader serotype coverage such as PCV13 and early initiation of cART would be desirable to maximize the protection against IPD in HIV-infected adolescents and adults.

Immunogenicity Studies of PCVs in HIV-infected Adults

Efficacy, immunogenicity and safety of PCVs in the HIV-infected individuals were recently reviewed by Nunes and Madhi[51] and Cordonnier et al.[52] Published studies to examine the immunogenicity of PCVs in the HIV-infected adults using different strategies are updated in **Table 2**[33,35,36,39-41,39-41,53-61] Similar to those observed in the immunogenicity studies of PPV23, direct comparisons between these studies and attempts to draw conclusions are confounded by the fact that the studies are heterogeneous in the vaccination schedule adopted (PCV alone or prime-boost vaccination with PCV followed by PPV, vaccine dose and interval between 2 vaccinations), time point of assessing serological response, the definitions used for serological responses (**Table 2**). While the correlation between the serological responses and clinical protection against IPD for adults is lacking, the antibody threshold used to define immune response in these studies is either ≥0.35 μg/ml or ≥1 μg/ml.

PCV as Primary Vaccination and the "Prime-boost" Strategy

Most of the published studies showed better immunogenicity of PCVs compared to PPV23 in HIV-infected adults[36,53,60,61] and a "prime-boost" strategy has been adopted to improve immunogenicity of PCV by combining a prime with a PCV followed by a boost with PPV23 4 to 8 weeks apart, although not all studies demonstrated supporting evidence for this "prime-boost" strategy.[36,53,57,60]

The case-control study by Lu et al enrolled 208 HIV-infected adults to receive either one dose of PCV7 or PPV23 who were matched by CD4 count and plasma HIV RNA load at vaccination.[61] Patients who received PCV7 maintained significantly higher immune responses to one or 2 of the 4 serotypes assessed than those who received PPV23 at both 24 and 48 weeks after vaccination.[61]

The randomized controlled trial by Lesprit et al enrolled 212 HIV-infected adults who received either PCV7 followed by PPV23 4 weeks later (prime-boost group) or PPV23 alone at week 4.[36] At week 8, the immune responses were higher in the prime-boost group, compared to the PPV23 group, and the superiority of immune responses sustained until 24 weeks after the first vaccine dose.[36]

In the randomized trial by Feikin et al that enrolled 67 HIV-infected adults to receive 2 doses of vaccines and/or placebo (PCV7-PCV7, PCV7-PPV23, placebo-PPV23 and placebo-placebo groups) given at an 8-week interval,[53] subjects receiving PCV7-PCV7 and PCV7-PPV23 had higher antibody concentrations and OPA titers compared with those receiving placebo-PPV23 at 8 weeks after the second vaccine dose. However, booster vaccination with either PCV7 or PPV23 following the first PCV7 dose did not further increase the immune responses.[53] The most recent trial by Ho et al showed similar findings. In this study, 331 HIV-infected adults were enrolled to receive 2 doses of PCV7, PPV23 or placebo given 60 d apart (PPV23-placebo, PCV7-placebo, PCV7-PPV23).[60] Patients receiving primary vaccination with PCV7 had better immune responses than those with PPV23 (in 2 of the 3 serotypes assessed) at both 60 and 180 days, but no differences were observed between the PCV-placebo and PCV-PPV23 groups.[60]

On the other hand, the randomized trial by Penaranda et al that enrolled 202 HIV-infected adults to receive either one dose of PCV7 followed by PPV23 4 weeks later or one dose of PPV23 alone (similar design to the study by Lesprit et al[36]) did not demonstrate any significant difference in the immune responses between the 2 groups.[57]

In summary, while vaccination adopting the "prime-boost" strategy with PCV followed by PPV23 tends to elicit better immune responses in HIV-infected adults, more studies are

Table 2. Immunogenicity studies of pneumococcal conjugate vaccine (PCV) in HIV-infected adults

Reference	Study period	Design	Study vaccines and schedule	Comparators (subject number)	% of CD4 ≥200 cell/μl	% on ART (or cART)	% of PVL <detection limit	Previous PPV or PCV	Timing of sampling	Methods (serotypes assessed)	Definition of responders	Results
[33]	1993	Randomized	[a] PCV5 (D0) [b] PPV23 (D0)	[a] HIV (+) (92) & HIV (-) (49) vs [b] HIV (+) (91) & HIV (-) (50)	51%	48%	NA	No PPV in the past 5 years	D0, D30	ELISA (6B, 14, 18C, 19F, 23F)	2-fold rise	PCV5 and PPV23 elicited similar antibody responses in HIV-infected patients
[35]	NA	Cohort	[a] PCV4 (D0)+ PCV4 (D30) + PPV23 (D300) [b] Historical controls: PPV23 (D0)	[a] HIV (+) (30) & HIV (-) (9) vs [b] HIV (+) (50) & HIV (-) (10)	47.5%	67.5% (CD4 <200: 100%; CD4 ≥200 : 32%)	NA	NA	D0, D30, D60, D300, D330 (Historical controls D0, D30)	ELISA (6B, 14, 19F, 23F)	GMC ≥ 1 μg/ml	PCV4 twice followed by PPV23 increased antibody responses compared to PPV23 alone, in both HIV-infected and uninfected patients
[36]	2002–2003	Randomized	[a] PCV7 (D0) + PPV23 (D28) [b] PPV23 (D28)	[a] (105) vs [b] (103)	100%	87% on cART	NA (Mean 2.21 vs 2.41 log_{10} copies/mL)	No PPV in the past 5 years	D0, D28, D56, D168	ELISA (4, 6B, 9V, 14, 18C, 19F, 23F and 1, 5)	2-fold rise and GMC ≥1 μg/ml	PCV7-PPV23 group had higher immune responses compared to PPV23 group at week 8 and 24
[39]	2008–2009	Cohort	PCV7 (D0) + PCV7 (D90) + PPV23 (D270) ± CPG 7909 to each vaccine * PCV7: double dose	ART (-) (20) vs ART (+) (75)	100%	79% on cART	79% (<50)	No PPV in the past 5 y (3 received PPV23 more than 5 y earlier)	D0, D90, D120, D270, D300	ELISA (4, 6B, 9V, 14, 18C, 19F, 23F); OPA (6B, 14, 19F, 23F)	2-fold rise to ≥5 serotypes with GMC ≥1 μg/ml	HIV-infected adults on cART achieved a more durable antibody response than cART-naive individuals
[40]	2004–2007	Cohort	PCV7 or PPV23	Immediate group (before initiating ART) (42) vs delayed group (after initiating ART with CD4 >200 or ART for 6 months) (37)	0% (at enrollment)	47%	NA	No prior vaccination	D0, D30, D180, D360	GMC (4, 6B, 9V, 14, 18C, 19F, 23F); OPA (14, 18C, 19F, 23F)	2-fold rise in GMC	Patients delayed to receive vaccination after the immune reconstitution with ART produced a higher antibody response
[41]	2005–2007 and 2008–2010	Cohort	Revaccination with [a] PPV23 (D0) [b] PCV7 (D0) [c] PCV7 (D0) + PCV7 (D28)	[a] (127) vs [b] (50) vs [c] (44)	94%	96% on cART	83% (<40)	PPV vaccinated ≥ 5 y earlier (mean: 5.8 years)	D0, D84, D168, D252, D336	ELISA (6B, 14, 19F, 23F)	2-fold rise to ≥2 serotypes with GMC ≥1 μg/ml	Revaccination with 2 doses of PCV7 achieved higher antibody responses compared to one dose of PCV7 or PPV23 throughout week 12 to week 48

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Table 2. Immunogenicity studies of pneumococcal conjugate vaccine (PCV) in HIV-infected adults *(Continued)*

Reference	Study period	Design	Study vaccines and schedule	Comparators (subject number)	% of CD4 ≥200 cell/μl	% on ART (or cART)	% of PVL <detection limit	Previous PPV or PCV	Timing of sampling	Methods (serotypes assessed)	Definition of responders	Results
[53]	1998–1999	Randomized	[a] PCV7 (D0) + PCV7 (D56) [b] PCV7 (D0) + PPV23 (D56) [C] Placebo (D0) + PPV23 (D56) [d] Placebo (D0) + Placebo (D56)	[a] (15) vs [b] (18) vs [c] (16) vs [d] (18)	100%	73% (42% on cART)	NA	No PPV in the past 5 years	D0, D56, D112	ELISA and OPA (4, 6B, 6V, 14, 23F)	2-fold rise in GMC or 4-fold rise i n OPA	PCV7-PCV7 and PCV7-PPV23 groups had higher antibody responses and OPA titers compared to placebo-PPV23 group; but booster vaccination with either PCV7 or PPV23 did not further increase the immune responses
[54]	2001–2002	Randomized	PCV7 (D0) + PCV7 (D28)	Past PPV recipients (54) vs Past placebo recipients (55)	NA (Median 313 vs 177 at the time of PCV vaccination)	0%	NA	Past PPV or placebo (time from previous PPV/ placebo: median [range], 62 [42–79] months)	D0, D28, D56	ELISA (4, 6B, 9V, 14, 18C, 19F, 23F)	2-fold rise, GMC >0.35 or >1 μg/ml	Past receipt of PPV did not affect vaccine response
[55]	2005	Cohort	PCV7 (D0) + PPV23 (D60)	HIV (+) (58) vs HIV (-) (29)	100%	0%	0%	NA	D0, D60, D90, D240	ELISA and OPA (4, 14)	GMCs, OPA titers ≥8	PCV elicited significant increases in antibody levels and OPA titers in HIV-infected patients without ART
[56]	2006–2008	Randomized	Revaccination with [a] PCV7 (D0) [b] PPV23 (D0)	[a] HIV (+) (131) & HIV (-) (25) vs [b] HIV (+) (73)	97%	82% on cART	68% (<50)	HIV (+): PPV vaccinated 3–8 y earlier (median 4.6 years) HIV (-): no prior vaccination	D0, D14, D60, D180	ELISA (4, 9V, 14, 19F)	2-fold rise to ≥2 serotypes with GMC ≥1 μg/ml	Revaccination with PCV7 elicited better immune response than PPV23 at day 14 and 60, but the superiority did not sustain to day 180
[57]	2007–2008	Randomized	(a) PCV7 (D0) + PPV23 (D28) (b) PPV23 (D28)	[a] (102) vs [b] (100)	100%	95% on cART	81%	No prior vaccination	D0, D28, D56	ELISA and avidity (4, 6B, 9V, 14, 18C, 19F, 23F)	2-fold rise and GMC ≥1 μg/ml	No difference in the antibody responses between 2 groups
[58]	2008–2009	Randomized	PCV7 (D0) + PCV7 (D90) +	CPG 7909 (48) vs	100%	79% on cART	79% (<50)	No PPV in the past 5 y		ELISA (4, 6B, 9V,		The addition of CPG 7909 (a TLR9 agonist)

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Table 2. Immunogenicity studies of pneumococcal conjugate vaccine (PCV) in HIV-infected adults *(Continued)*

Reference	Study period	Design	Study vaccines and schedule	Comparators (subject number)	% of CD4 ≥200 cell/μl	% on ART (or cART)	% of PVL <detection limit	Previous PPV or PCV	Timing of sampling	Methods (serotypes assessed)	Definition of responders	Results
			PPV23 (D270) * PCV7: double dose	placebo (49) to each vaccine				(3 received PPV23 more than 5 y earlier)	D0, D90, D120, D270, D300	14, 18C, 19F, 23F, and 1, 7F, 19A); OPA (6B, 14, 19F, 23F)	2-fold rise to ≥5 serotypes with GMC ≥1 μg/ml	to PCV7 enhanced the proportion of vaccine high responders
[59]	2008–2010	Cohort	[a] PCV7 (D0) + PCV7 (D28) [b] PCV7 (D0)	[a] (115) vs [b] (114)	87%	72% on cART	46% (<40)	No prior vaccination	D0, D84, D168, D252, D336	ELISA (6B, 14, 19F, 23F)	2-fold rise with GMC ≥1 μg/ml	Two doses of PCV7 achieved better antibody responses than one dose during 48 weeks of follow-up
[60]	2005–2009	Randomized	[a] PPV23 (D0) + placebo (D60) [b] PCV7 (D0) + placebo (D60) [c] PCV7 (D0) + PPV23 (D60)	[a] (111) vs [b] (110) vs [c] (110)	100%	77% on cART	68% (<400)	No prior vaccination	D0, D60, D180	ELISA (6B, 9V, 14)	4-fold rise	Primary vaccination with PCV7 had better antibody responses than PPV23, but no differences was observed between the PCV-placebo and PCV-PPV23 groups
[61]	2000–2002 and 2008–2010	Cohort	[a] PPV23 (D0) [b] PCV7 (D0)	[a] (104) vs [b] (104)	83%	86% on cART	72% (<400)	No prior vaccination	D0, D168, D336	ELISA (6B, 14, 19F, 23F [PCV] 14, 19F, 23F [PPV])	2-fold rise to ≥2 serotypes with GMC ≥1 μg/ml	PCV7 achieved better antibody responses than PPV23 at week 48

Note: * subject number: HIV-infected patients if not specified

Abbreviations: ART, antiretroviral therapy; cART, combination antiretroviral therapy; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean antibody concentrations; NA, not available; OPA, opsonophagocytic activity; PCV7, 7-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; PVL, plasma HIV RNA load

warranted to determine the best time interval between the doses to optimize the vaccine effectiveness.

PCV Revaccination in HIV-infected Adults who have Received PPV Before

Before the introduction of PCVs, most HIV-infected patients received primary PPV vaccination and revaccination with PPV23 when 5 y has elapsed after the primary vaccination based on clinical guidelines for prevention of opportunistic infections.[30] However, a prior randomized clinical trial by Tasker et al has shown that the immunogenicity of PPV23 revaccination more than 5 y after the initial dose was very limited.[62] Significant decline in immune responses was observed in HIV-infected patients receiving cART 5 y after primary vaccination with PPV23, especially in patients with CD4 <100 cells/μl and uncontrolled HIV replication.[38] Therefore, several studies have examined the immunogenicity of revaccination with PCV in HIV-infected patients who have received PPV before.[41,54,56]

The first study in Uganda by Miiro et al compared the immunogenicity of 2 doses of PCV7 (4 weeks apart) versus placebo in HIV-infected adults who have received PPV23 3.5 to 6.6 y (median 5.2 years) earlier.[54] Significant increases in antibody concentrations to all vaccine serotypes were observed after revaccination with PCV7, but no difference in immune response was found by past vaccination status, suggesting that past receipt of PPV23 did not blunt the immune response to PCV7.[54]

In the randomized trial by Crum-Cianflone et al, vaccination with PCV7 in HIV-infected adults who had previously received PPV23 3 to 8 y earlier (median 4.6 years) temporarily induced a better immune response than PPV23 at 14 and 60 d after vaccination, but this effect did not sustain to 180 d post-vaccination.[56] In another observational study by Lu et al, one or 2 doses of PCV7 (4 weeks apart) or PPV23 were administered in HIV-infected adults previously vaccinated with PPV23 5 y or more earlier. Revaccination with 2 doses of PCV7 resulted in a higher immune response rate to at least 2 of the 4 serotypes assessed compared to revaccination with one dose of PCV7 or PPV23 throughout week 12 to week 48.[41] The conflicting results between the 2 studies may be due to different serotypes assessed and lower baseline antibody levels among patients in the former study,[56] which may decrease the proportion of the participants who could achieve post-vaccination antibody levels to ≥1 μg/ml.

Association between CD4 Counts, cART, HIV Replication and Immune Responses to PCVs

The studies by Kroon et al and Miiro et al have shown that HIV-infected patients with CD4 counts ≥200 cells/μl had a higher immune response, either in absolute antibody concentrations[35,54] or fold rise in antibody levels[35], to PCV compared with those with CD4 <200 cells/μl. In contrast, Lu et al showed that among HIV-infected patients receiving cART, only successful suppression of HIV replication, but not CD4 counts ≥200 cells/μl at vaccination, was associated with better immune responses.[61] For patients with CD4 >200 cells/μl, the studies by Feikin et al and Sogaard et al found no significant association between immune response to PCV and CD4 counts.[39,53]

Two studies evaluated the effect of antiretroviral therapy on immune responses to PCV.[39,40] Among the HIV-infected patients with CD4 <200 cells/μl, the study by Slayter et al enrolled 2 groups of patients who received PCV7 or PPV23 either immediately or delayed the vaccination until their immunity had been reconstituted with antiretroviral therapy (CD4 >200 cells/μl or receipt of antiretroviral therapy for 6 months).[40] The results showed that patients who delayed the vaccination after the immune reconstitution with antiretroviral therapy achieved a better immune response than those who underwent vaccination immediately. Another study by Sogaard et al which enrolled HIV-infected patients with CD4 >200 cells/μl also found that, after receiving a double dose of PCV7 administered twice at 3 months apart, cART-experienced and cART-naïve HIV-infected adults had similar immune responses initially, but cART-experienced patients achieved a more durable immune response of higher magnitude and functional activity than cART-naïve patients at 9 months.[39] The superiority persisted after adjustment for CD4 counts (≥500 or 200–499 cells/μl).[39]

In summary, in the era with improved access to cART worldwide and as cART is recommended to be initiated earlier by all of the clinical guidelines,[48,61,63] it may be preferable to provide PCVs to HIV-infected adults after the HIV replication is successfully suppressed with cART.

Other Strategies to Improve the Immunogenicity of PCV in HIV-infected Adults

The addition of an adjuvant CPG 7909, a toll-like receptor agonist, has been evaluated by Sogaard et al to improve the immunogenicity of pneumococcal vaccines in the HIV-infected adults.[58] Participants received double doses of PCV7 twice at 0 and 3 months and one dose of PPV23 at 9 months, along with 1 mg of CPG 7909 added to each of the 3 vaccine doses. The proportion of high vaccine responders (defined as a fold2-increase in antibody levels to ≥ 1 μg/ml, for at least 5 of 7 serotypes examined) was higher in the CPG 7909 group than placebo group at 4, 9 and 10 months post-vaccination. OPA titers were also elevated in the CPG 7909 group. In contrast, the addition of CPG 7909 to PPV23 did not enhance the antibody response to non-PCV7 serotypes.

The Impact of the Introduction of PCV in Children

The introduction of PCV in children has reduced the incidence of IPD in adults including high risk populations, which was thought to be due to "herd" effect.[64–66] Prior studies

among HIV-infected individuals also reported significant declines in the incidence of IPD in HIV-infected adults after the implementation of PCV7 in children.[67–70] However, this change has been accompanied by increases in the incidence of IPD by non-vaccine serotypes, such as serotypes 3, 6A, 19A.[67,68] As a result, one might expect that the introduction of PCV13 with broader serotype coverage into the routine vaccination schedule for children will result in further declines in IPD among HIV-infected adults.[71]

Conclusions

With cART, the survival of HIV-infected adults have significantly been prolonged,[72,73] and when and what vaccine and the doses to be administered as revaccination in the lifetime of HIV-infected adults has become clinically relevant for further investigation. With introduction of PCVs with a broader serotype coverage and widespread, early initiation of cART, strategies for preventing pneumococcal pneumonia or IPD in the HIV-infected adults have evolved. PCV13 has replaced PPV23 in primary vaccination, followed 8 weeks later by revaccination with PPV23 in the guidelines.[46,47] Given the fact that the follow-up duration of published immunogenicity studies of PCV7 vaccination in HIV-infected adults being at most 12 months,[61] the durability of immune responses to the recommended prime-boost strategy with PCV13 followed by PPV23 warrants further studies to determine the optimal vaccines and intervals for subsequent revaccinations during the lifetime.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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