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Review

Pneumococcal Vaccination Strategies Among HIV-infected Adult Patients: A Review of the Literature

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Abstract. *Background/Aim: Streptococcus pneumoniae is the leading cause of bacterial pneumonia and an important cause of invasive disease. Despite the antiretroviral therapies, adults infected with human immunodeficiency virus (HIV) are at particular risk for invasive pneumococcal disease (IPD). The purpose of this study was to report the efficacy of the strategies currently being used in pneumococcal vaccination for HIV-infected adults. Materials and Methods: A literature search was performed through electronic databases, for original articles in English, from years 2000 to 2019. Clinical trials controlled or randomized, and cohort studies were included. Results: While 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for immunocompromised patients, it has been reported that it is less suitable for HIV-infected patients. Recent guidelines have added pneumococcal conjugate vaccine (PCV) to the list of recommended vaccines. Conclusion: Further studies are needed to determine the optimal vaccines and intervals for subsequent revaccinations during the lifetime.*

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Streptococcus pneumoniae is a bacterium with more than 90 known subtypes that colonizes the upper respiratory tract and is a frequent element of the normal flora of the nasopharynx of children (up to 65% in nursery babies) and to a lesser extent of adults (15%). It is a major cause of morbidity and mortality in children and adults worldwide. Children less than 5 years of age – mainly infants and toddlers up to 2 years of age, followed by adults over 55-65 years of age.

Pneumococcal disease is caused by either person-to-person transmission mainly by respiratory droplets (sneezing, coughing) or by conversion of simple colonization into infection in conditions of decreased body defenses *e.g.* due to fusion, cold, immunosuppression, smoking *etc.* It causes both non-invasive infections such as acute otitis media, pneumonia and sinusitis, and serious invasive infections such as septicemia, meningitis and severe pneumonia with bacteremia and/or impotence. In adults, the most common clinical manifestation of pneumococcal infection is pneumonia, which accounts for 36% of community-acquired pneumonia and 50% of hospital pneumonia.

Of course, it is common knowledge that lower respiratory tract infections are a major factor in morbidity and mortality. In particular, the case-fatality rate of pneumococcal pneumonia is 5-7% and may be much higher among elderly persons (1). Only in the USA, the cost of hospitalization is charged to the health budget by $1.3-2.2 billion a year. Globally, pneumococcal disease accounts for 1.6 million deaths a year, particularly affecting people of older ages. In Europe, the incidence of pneumococcal pneumonia appears to be greater than in the other continents (2). In 2050, the proportion of people aged over 65 in Europe will reach

30.3% (2000, 15.7%), therefore it is easy to see that prevention of pneumococcal disease is more beneficial than treatment.

The fundamental means of prevention is the preparation and extensive administration of a safe and effective vaccine. The US Centers for Disease Control recommended, since the 80's, using the 23-valent pneumococcal polysaccharide vaccine (PPV23) for immunocompromised subjects. This vaccine contains purified polysaccharide antigens of the pneumococcal capsule and covers the 23 strains responsible for 88% of cases of bacteremia disease. The development of immunity, including increased opsonization, phagocytosis and microbial killing, is achieved through the activation of B-cells. Because the production of antibodies from this vaccine is independent of T-cell activation, no immune memory is induced, mucosal immunity is not increased, and its repeated administration does not provide a booster effect. Vaccine safety has been proven beyond doubt as its most common side effects include mild and self-limiting local reactions. In contrast to safety, the clinical efficacy of the vaccine has been challenged since several studies have shown that in elderly or immunosuppressed patients, as well as in cohorts, there is insufficient production of antibodies whose functional activity is less than the desired (3-5). Other studies – but not all – have concluded that the gradual decrease in antibody titer 5-10 years after initial vaccination with PPV23 does not return to baseline after repeated administration of the same vaccine (6). Similarly, the results of clinical trials have shown completely contradictory results (7). In some publications, the polysaccharide vaccine appears to provide significant protection against the risk of developing non-bacteremic pneumonia, while in others (mainly migraine) this protection appears to be minimal, if not zero (8, 9). The ability to prevent PPV23 from its bactericidal forms of pneumococcal disease is reported as being measurable in all adults (63-83%) but very low in the high risk (0-42%) (10). It should be noted that a newly published eight-year long epidemiological study from two regions of the United Kingdom showed an increase in incidence of invasive pneumococcal disease despite an improvement in vaccination rates with PPV23 from 49% to 70% (11).

However, another very recent prospective study, in more than 27,000 patients over 60 years of age, in its precursor report, claims that PPV23 offers some protection against ischemic stroke and myocardial infarction (12). The exact mechanism that is subject to this protective action is unknown, although various assumptions have been made.

It has also been reported that PPV23 booster causes "hyporesponsiveness". Due to this limitation, PPV23 is less suitable for HIV-infected individuals, mainly for those in advanced stages of immunodeficiency. More recent guidelines have added conjugated polysaccharide vaccine (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.

The PCV exhibits an almost totally consistent positive correlation. It is well known that coupled vaccines stimulate both B- and T-cells, causing intense immunostimulation and immune memory. Although PCV was introduced as a 7-valent only in 2000, it has dramatically reduced peripheral bacteremic disease and nasal pneumococcal prolapse in children, with unwanted events moving to PPV23 levels.

Its action on the nasal passage resulted in a reduction in transmission and subsequent pneumococcal disease in anesthetized adults. This phenomenon is known as "herd immunity" (13). Equally impressive is the fact that vaccination with PCV also reduced the incidence of pneumonia, demonstrating the bi-directional relationship between the pneumococcus and the viruses in the pathogenesis of the disease (14).

Despite the fact that the antiretroviral therapy helps reconstitute the immune system and suppress HIV, patients with HIV are still at higher risk for pneumococcal disease in comparison to the general population. Therefore, physicians, based on researches and studies conducted so far, suggest that in order to reduce the risk of pneumococcal disease in adults infected by HIV the PPV23 composed of T-cell-independent antigens could be used (15). However, the results of studies that examine the serological responses to PPV23 are conflicting because of the heterogeneity of study design, execution and subjects enrolled. On the other hand, there is moderate evidence to support the routine use of PPV23 in HIV-infected adults according to observational studies of clinical effectiveness. Furthermore, PCV with conjugation of the capsular polysaccharide to a protein carrier, has been shown to have better results on the immune system than PPV23 and to protect HIV-infected children against pneumococcal disease and HIV-infected adolescents and adults against recurrent invasive pneumococcal disease (16, 17). The recent guidelines recommend that HIV-infected patients older than 19 years old receive one dose of 13-valent pneumococcal conjugate vaccine (PCV13) followed by a booster vaccination with PPV23 (15). However, assessment of the efficacy and subsequent widespread acceptance of the PCV13/PPV23 sequential administration prime-boost strategy is dependent on the outcome of clinical trials in the setting of HIV infection which may take several years to complete (18).

The purpose of this article was to provide a review on the efficacy of the strategies currently being used in pneumococcal vaccination for HIV-infected adults.

Materials and Methods

A research was conducted in electronic databases, for original articles in the English or Greek language, from years 2000 to 2019.

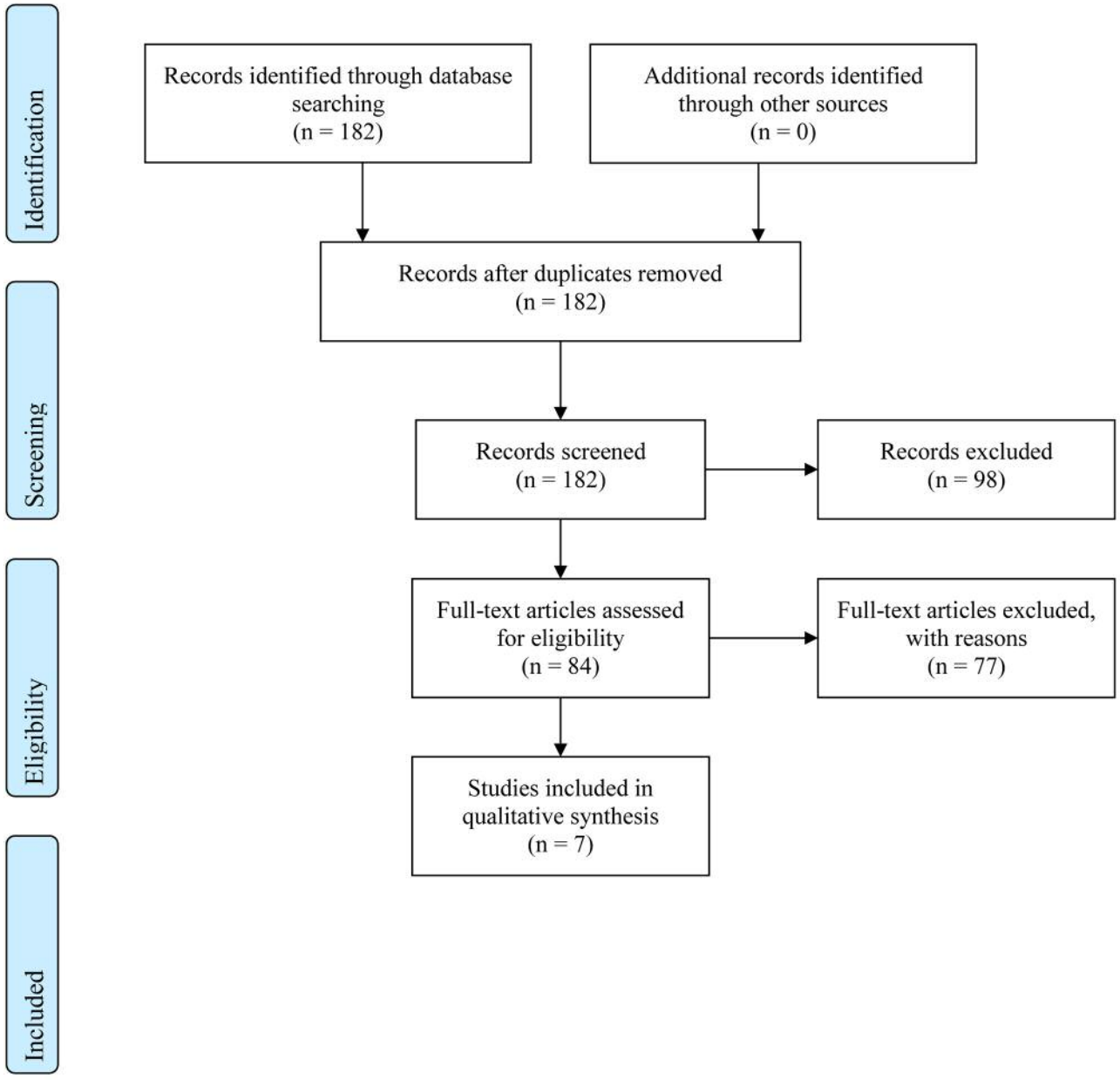

Figure 1. *Prisma flow diagram for study identification and selection.*

Clinical trials, controlled or randomized, and cohort studies were included.

The following electronic databases were used for the research: PubMed, Scielo, Elsevier, and Google Scholar. After exclusion of duplicated articles, an analysis of the titles of the studies was carried out; those articles that did not address adult HIV patients were excluded. The next step was the analysis of the abstracts of the articles which excluded those that were not related to the review goals. The research method for the articles is illustrated in the Prisma diagram below (Figure 1, Table I).

Results

French *et al*. conducted the only clinical efficacy trial on PCV7 in adults and adolescents. They enrolled 496 Malawians ≥15 years old of whom 437 (88%) were HIV-infected, who had recovered from IPD. The participants received two doses of PCV7, or placebo administered four weeks apart. The researchers where mainly interested in recurrent episodes of IPD caused by vaccine serotypes or

Table I. *Studies included in the literature review.*

Author	Year	Patients	Study	Results
Lu *et al*. (20)	2013	208 HIV-infected adults	One dose of PCV7 or PPV23	At week 48, patients who received PCV demonstrated a statistically significant higher response rate to at least 2 serotypes than those who received PPV (37.5% *vs*. 20.2%, p=0.006).
Lesprit *et al*. (21)	2007	212 HIV-infected adults	Either PCV at week 0 and PPV at week 4 (n=106) or PPV alone at week 4 (n=106).	At week 8, the profile of response was better in the prime-boost group compared to the PPV group. Early differences between groups remained significant at week 24 (proportional OR=2.14; 95%CI=1.30-3.54; p=0.003).
Feikin *et al*. (22)	2001	67 HIV-infected adults	2 doses of vaccines and/or placebo (PCV7-PCV7, PCV7-PPV23, placebo-PPV23 and placebo-placebo groups) given at an 8-week interval	Patients receiving conjugate-conjugate and conjugate-polysaccharide had higher antibody concentrations (serotypes 4, 6B, 9V and serotype 23F, respectively) and opsonophagocytic titers (functional antibody assay, serotypes 9V, 23F and serotypes 4, 6B, 9V, respectively) after the second dose (p<0.05).
Ho *et al*. (23)	2013	331 HIV-infected adults	2 doses of PCV7, PPV23 or placebo given 60 days apart (PPV23-placebo, PCV7-placebo, PCV7-PPV23)	A greater proportion of PCV7 recipients reached and sustained IgG antibody concentrations at least four times as high as those at baseline, for serotypes 6B and 9V. A PPV23 dose after PCV7 did not enhance immunogenicity.
Penaranda *et al*. (24)	2010	202 HIV-infected adults	PCV and PPV 4 weeks after *vs*. PPV alone.	There were no differences in the two strategies, either in the percentage of IgG two-fold increase for the PCV included serotypes or IgG two-fold increase, reaching the level of 1mg/ml except for serotype 23F (26% responded after PCV and PPV *vs*. 14% after PPV).
Marcus *et al*. (25)	2016	13,079 HIV-infected and 137,643 HIV-uninfected adults	PPV23	PPV23 was not significantly associated with a reduced risk of IPD among HIV-infected or HIV-uninfected patients, with a high prevalence of PPV23-covered serotypes among HIV-infected IPD cases. Both HIV-uninfected and HIV-infected patients may have benefited indirectly from PCV7 and PCV13 among children, licensed in 2000 and 2010, respectively.
Sogaard *et al*. (26)	2010	99 HIV-positive patients	Double doses of PCV7 at 0 and 3 months and 1 dose of PPV23 at 9 months, with experimental patients receiving 1 mg of CPG 7909 added to each of their 3 vaccine doses	The proportion of vaccine high responders was higher in the experimental group (n=48) than among controls (n=49; 48.8% *vs*. 25.0%; p=0.02) at 9 months. Greater proportions of high responders were also observed at 3 (51.1% *vs*. 39.6%; p=0.26), 4 (77.3% *vs*. 56.3%; p=0.03), and 10 months (87.8% *vs*. 51.1%; p<0.001).

HIV: Human immunodeficiency virus; PCV7: 7-valent pneumococcal conjugate vaccine; PPV23: 23-valent pneumococcal polysaccharide vaccine; PCV: pneumococcal conjugate vaccine; PPV: pneumococcal polysaccharide vaccine; PCV13: 13-valent pneumococcal conjugate vaccine.

serotype 6A. The follow-up of 1.2 years (on average) showed 67 episodes of IPD in 52 HIV-infected patients. Those episodes occurred mainly in the subgroup of participants with CD4 count <200 cells/ml at base-line. In HIV-infected patients, the vaccine efficacy was 85% in the first-year post-vaccination, decreased to 74% at the follow-up and dropped down to 25% thereafter. Moreover, patients with a CD4 count <200 cells/ml at baseline had 7.1-fold greater risk for developing recurrent IPD than those with a CD4 count >500 cells/ml. In the study of French *et al*., only 50% of the episodes of IPD in the placebo group were attributed to *Streprococcus pneumoniae* of vaccine serotypes and serotype 6A. In addition, only 13% of HIV-infected participants were receiving combination antiretroviral therapy (cART) at baseline. The conclusion was that, in order to protect, at the maximum, adolescents and adults infected by HIV against IPD, PCVs with broader serotype coverage such as PCV13 and early initiation of cART should be the first choice (19). Overall, 208 HIV-infected adults participated in the case-control study by Lu *et al*. and they

received either one dose of PCV7 or PPV23, and were matched by CD4 count and plasma HIV RNA load at vaccination. The results showed that significantly higher immune responses to one or two of the four serotypes assessed were maintained by patients who received PCV7 in comparison to those who received PPV23 at both 24 and 48 weeks after vaccination (20).

In the randomized controlled trial by Lesprit *et al*., 212 HIV-infected adults took part and they received either PCV7 followed by PPV23 4 weeks later (prime-boost group) or PPV23 alone at week 4. Results showed that at week 8, the prime-boost group had higher immune responses, compared to the PPV23 group, and these results remained even until 24 weeks after the first vaccine dose (21).

In the randomized trial by Feikin *et al*., 67 HIV-infected adults were enrolled, and they received two doses of vaccines and/or placebo given at an 8-week interval. Higher antibody concentrations and OPA titers occurred to those receiving PCV7-PCV7 and PCV7-PPV23 in comparison to those receiving placebo-PPV23 at 8 weeks after the second vaccine dose. However, the immune responses were not further increased with booster vaccination with either PCV7 or PPV23 following the first PCV7 dose (22).

Similar findings have been reported in a recent trial by Ho *et al*. A total of 331 HIV-infected adults participated in this study receiving two doses of PCV7, PPV23 or placebo given 60 days apart. Better immune responses were observed in patients receiving primary vaccination with PCV7 compared to those with PPV23 (in two of the three serotypes assessed) at both 60 and 180 days. However, the PCV-placebo and PCV-PPV23 groups showed no differences between them (23).

No significant difference in the immune responses between the two groups was also observed in the randomized trial by Penaranda *et al*. In this trial, 202 HIV-infected adults received either one dose of PCV7 followed by PPV23 four weeks later or one dose of PPV23 alone (24). Marcus *et al*. conducted a cohort study comparing adults infected by HIV to demographically matched HIV-uninfected adults. According to their results, there was no association of the 23-valent pneumococcal polysaccharide vaccination to a reduced risk of IPD in both groups (25).

Finally, Sogaard *et al*., evaluated the addition of an adjuvant CPG 7909, a toll-like receptor agonist, in order to improve the immunogenicity of pneumococcal vaccines in the HIV-infected adults. Participants of the study 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. There were more high vaccine responders in the CPG 7909 group than in the placebo group at 4-, 9- and 10-months post-vaccination and the OPA titers were also higher. In contrast, the study found that adding CPG 7909 to PPV23 did not enhance the antibody response to non-PCV7 serotypes (26).

Conclusion

The introduction of PCVs with a broader serotype coverage and widespread, early initiation of cART, resulted in an evolution of strategies for preventing pneumococcal pneumonia or IPD in the HIV-infected adults. The guidelines have replaced PPV23 in primary vaccination with PCV13, followed 8 weeks later by revaccination with PPV23. However, the immunogenicity studies of PCV7 vaccination in HIV-infected individuals have a follow-up duration of at most 12 months and thus we cannot have conclusive observations about the sustainability of the immune responses. Further studies should be conducted in order to determine the durability of immune responses to the recommended prime-boost strategy with PCV13 followed by PPV23 and the optimal vaccines and intervals for subsequent revaccinations during the lifetime.

Conflicts of Interest

The Authors declare that there is no conflict of interest regarding this study.

Authors' Contributions

ED designed the study and wrote the article. AG, CD, NG and AP collected the data. AG, CD, NG, AP and SS offered scientific advice. AG, CD, NG and NG revised the article.

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