

Effectiveness of Polysaccharide Pneumococcal Vaccine in HIV-Infected Patients: A Case-Control Study

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Background. Polysaccharide pneumococcal vaccine (PPV) is recommended among human immunodeficiency virus (HIV)-infected patients, although its effect in reducing the incidence of pneumonia or invasive pneumococcal disease is not well established. Our objective was to determine the effectiveness of 23-valent PPV in HIV-infected adults and the risk factors for pneumococcal pneumonia or invasive pneumococcal disease.

Methods. We performed a retrospective case-control study in 4 Spanish hospitals for the period from January 1995 through December 2005 using the HIV database from each hospital to identify case patients with *Streptococcus pneumoniae* disease and control subjects without a history of pneumococcal infection.

Results. A total of 184 case patients and 552 control subjects were identified. The factors associated with pneumococcal disease in bivariate analysis were active injection drug use (odds ratio [OR], 3.33; 95% confidence interval [CI], 2–5.55), alcoholism (OR, 3.03; 95% CI, 1.86–4.91), chronic obstructive pulmonary disease (OR, 2.58; 95% CI, 1.3–5.1), cirrhosis (OR, 6.05; 95% CI, 3.2–11.4), antiretroviral therapy (OR, 0.23; 95% CI, 0.16–0.32), trimethoprim-sulfamethoxazole prophylaxis (OR, 0.66; 95% CI, 0.45–0.97), viral load <5000 copies/mL (OR, 0.38; 95% CI, 0.26–0.54), and previous PPV (OR, 0.39; 95% CI, 0.24–0.65). Risk factors for pneumococcal disease in multivariate analysis were cirrhosis (OR, 5.64; 95% CI, 2.53–12.53), chronic obstructive pulmonary disease (OR, 2.90; 95% CI, 1.21–6.94), and alcoholism (OR, 2.15; 95% CI, 1.11–4.19), whereas protective factors were receipt of antiretroviral therapy (OR, 0.23; 95% CI, 0.14–0.36) and receipt of pneumococcal vaccine (OR, 0.44; 95% CI, 0.22–0.88), even in patients with CD4 lymphocyte counts <200 cells/ μ L.

Conclusions. Antiretroviral therapy and PPV have a significant, independent protective effect against pneumococcal disease, regardless of CD4 lymphocyte count; thus, all patients with HIV infection should be vaccinated with PPV to prevent pneumococcal disease.

In the HAART era, cases of bacterial pneumonia still occur in HIV-infected patients [1, 2]. As it is in the general population, *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia among HIV-infected adults, who have rates of bacteremia that are higher than those observed in non-HIV-infected subjects [3–6].

Although some studies have reported a decrease in the incidence of invasive pneumococcal disease among HIV-infected patients after the widespread introduction of HAART [3, 7–10], other studies did not find this

tendency [11, 12]. Nevertheless, even in the former studies, the incidence of invasive pneumococcal disease among HIV-infected adults is still higher than the incidence among similarly aged non-HIV-infected adults [5, 6, 10]. Several factors, such as injection drug use, chronic liver disease, alcohol abuse, cigarette smoking, and poor adherence to antiretroviral therapy, have been associated with the risk of pneumococcal disease [7,11]. For these reasons, 23-valent polysaccharide pneumococcal vaccine (PPV) is currently recommended for HIV-infected patients, particularly those with CD4 lymphocyte counts >200 cells/ μ L [8, 13, 14]. However, the evidence supporting this recommendation is controversial, and the case-control studies [7–9, 13, 15, 16] and the only published randomized study [17] to have investigated the effect of this vaccine in preventing invasive pneumococcal disease produced conflicting results.

The aim of our study was to determine the effec-

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tiveness of the 23-valent PPV in preventing pneumococcal pneumonia or invasive pneumococcal disease among HIV-infected adults. Secondary objectives were to investigate the risk factors for pneumococcal disease among HIV-infected adults.

PATIENTS AND METHODS

Study population. A retrospective case-control study including HIV-infected adults with previous pneumococcal disease was performed during the period from 1 January 1995 through 31 December 2005 in 4 Spanish hospitals: Hospital Son Dureta (a 900-bed tertiary care teaching hospital that treats 2000 HIV-infected patients; Palma de Mallorca, Spain), Hospital Vall d'Hebron (a 1200-bed tertiary care teaching hospital that treats 1700 HIV-infected patients; Barcelona, Spain), Fundació Son Llatzer (a 350-bed secondary care teaching hospital that treats 500 HIV-infected patients; Palma de Mallorca, Spain), and Mutua de Terrasa (a 580-bed secondary care teaching hospital that treats 400 HIV-infected patients; Palma de Mallorca, Spain).

Case patients and control subjects. Case patients were identified from the databases of HIV-infected patients for each hospital. Case patients were defined as HIV-infected adults (age, ≥ 18 years) with a previous diagnosis of pneumococcal pneumonia or invasive pneumococcal disease from 1995 through 2005. Case patients for whom the CD4 lymphocyte count was unknown at the time of diagnosis or within 3 months before the diagnosis were excluded.

Three patient groups were defined: (1) the definite pneumococcal pneumonia group, which included patients with clinical symptoms and radiological signs of pneumonia and *S. pneumoniae* isolation from blood, pleural fluid, or sputum cultures with positive urinary pneumococcal antigen test results or $\geq 10^3$ cfu/mL in bronchoalveolar lavage samples obtained from fiberoptic bronchoscopy; (2) the presumptive pneumococcal pneumonia group, which included patients with clinical symptoms and radiological signs of pneumonia and *S. pneumoniae* isolation from sputum culture or a positive urinary antigen test result; and (3) the other pneumococcal infections group, which included patients with *S. pneumoniae* isolation from normally sterile sites.

Three control subjects without pneumococcal infection or bacterial pneumonia of unknown etiology were selected for each case patient and matched for the following variables: sex, age (age of the case patient at the time of pneumococcal disease diagnosis ± 5 years), CD4 lymphocyte count (CD4 lymphocyte count of the case patient at the time of pneumococcal disease diagnosis ± 50 cells/ μ L; if the CD4 lymphocyte count of the case patient was >500 cells/ μ L, control subjects were selected from among HIV-infected adults with CD4 lymphocyte counts >500 cells/ μ L), and , HIV infection risk factor (divided into injection drug use and other, including male-male sex, hetero-

sexual sex, receipt of a blood transfusion, and unknown transmission mechanism).

To identify the matched control subjects for each case patient, we divided the HIV databases from each hospital into different groups according to sex, CD4 lymphocyte count interval, and transmission mechanism. We then selected 3 control subjects for each case patient. For each stratum, we selected control subjects who followed the case patient in alphabetical order. Information about vaccination status was not visible at the moment of control subject selection.

Study variables. Once case patients and control subjects were identified, we reviewed clinical records and collected the following variables: age, sex, 23-valent PPV administration (Pneumo23; Sanofi Pasteur), date of vaccination (before the pneumococcal disease diagnosis for case patients and at any time during the study period for control subjects), risk factor for HIV infection, active injection drug use, current smoking (cigarettes), and active alcohol abuse (>80 g of alcohol ingested per day), CD4 lymphocyte count, HIV load, AIDS-defining illnesses, receipt of trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis, and macrolide prophylaxis, antiretroviral therapy (ART), hepatitis B virus and hepatitis C virus coinfection, presence of underlying diseases (such as chronic obstructive pulmonary disease [COPD], sickle cell anaemia, or cirrhosis), date of pneumococcal infection diagnosis for case patients, type of infection (definite pneumococcal pneumonia, presumptive pneumococcal pneumonia, or other pneumococcal infection), and results of blood or sputum cultures and urinary antigen tests.

Statistical analysis. Variables were analyzed with the statistical software package SSPS, version 11.0 (SPSS). First, we performed an analysis of the characteristics of the entire study population and separately performed another description in which the study population was analyzed in 2 groups: case patients and control subjects. We then conducted a bivariate analysis using χ^2 test with a significance level of .05 and a multivariate analysis using a forward-conditional binary logistic regression method that incorporated the variables associated with pneumococcal infection in the bivariate analysis.

RESULTS

From 1 January 1995 through 31 December 2005, 736 subjects were included in the study (184 case patients and 552 control subjects). The 23-valent PPV was administered to 151 (20%) of the 736 study subjects (20 [11%] of 184 case patients and 131 [24%] of 552 control subjects).

The characteristics of case patients and control subjects are summarized in table 1. Among the case patients, there were 117 definite pneumococcal pneumonia (64%), 44 presumptive pneumococcal pneumonia (24%) and 23 other pneumococcal infections (12%). In 127 (69%) of the case patients, there was

Table 1. Baseline characteristics of case patients and control subjects.

Variable	Case patients (n = 184)	Control subjects (n = 552)	P
Age, median years	38	38	1
Male sex	134 (73)	402 (73)	1
Smoking	137 (75)	235 (72)	.43
Alcohol abuse	36 (19.6)	41 (7.4)	<.001
Active injection drug use	37 (26.4)	41 (9.8)	.03
CD4 lymphocyte count, median cells/ μ L	204	210	.60
CD4 lymphocyte count \geq 200 cells/ μ L	95 (51.6)	291 (52.7)	.79
HIV load, median log copies/mL	4.5	2.8	.04
HIV load, <5000 copies/mL	60 (37.7)	309 (61.4)	<.001
AIDS-defining illness	70 (38)	190 (34)	.37
TMP-SMZ use	43 (23.4)	174 (31.5)	.04
Macrolide use	0	4 (0.7)	.24
ART use	79 (42.9)	422 (76.6)	<.001
HBV infection	15 (8.2)	33 (6)	1
HCV infection	130 (70.7)	390 (70.7)	1
COPD	16 (8.7)	19 (3.6)	.005
Cirrhosis	29 (15.8)	16 (3)	<.001
Receipt of 23-valent PPV	20 (10.9)	131 (23.8)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. ART, antiretroviral therapy; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus; HCV, hepatitis C virus; PPV, polysaccharide pneumococcal vaccine; TMP-SMZ, trimethoprim-sulfamethoxazole.

an associated bloodstream infection. The percentage of patients with positive microbiological test results is shown in table 2.

Factors associated with pneumococcal infection in bivariate analysis were active injection drug use (OR, 3.33; 95% CI, 2–5.55), active alcohol abuse (OR, 3.03; 95% CI, 1.86–4.91), COPD (OR, 2.58; 95% CI, 1.3–5.1), cirrhosis (OR, 6.05; 95% CI, 3.2–11.4), receipt of antiretroviral therapy (OR, 0.23; 95% CI, 0.16–0.32), receipt of TMP-SMZ prophylaxis (OR, 0.66; 95% CI, 0.45–0.97), viral load <5000 copies/mL (OR, 0.38; 95% CI, 0.26–0.54), and previous receipt of 23-valent PPV (OR, 0.39; 95% CI, 0.24–0.65). There was no relation between pneumococcal infection and sex, cigarette smoking, Centers for Disease Control and Prevention HIV infection stage, CD4 lymphocyte count, and hepatitis B virus or hepatitis C virus coinfection. Results are shown in table 3.

Factors associated with an increased risk of pneumococcal disease in the multivariate analysis were cirrhosis (OR, 5.64; 95% CI, 2.53–12.53), COPD (OR, 2.90; 95% CI, 1.21–6.94), and active alcohol abuse (OR, 2.15; 95% CI, 1.11–4.19), whereas protective factors were current receipt of HAART (OR, 0.23; 95% CI, 0.14–0.36) and having received 23-valent PPV (OR, 0.44; 95% CI, 0.22–0.88) (table 3).

When the study population was stratified by CD4 lymphocyte count (\geq 200 cells/ μ L vs. <200 cells/ μ L; median CD4 lymphocyte count, 325 cells/ μ L vs. 89 cells/ μ L), the 23-valent PPV was protective in both groups and achieved a stronger protective effect for pneumococcal infection in the group with a CD4

lymphocyte count <200 cells/ μ L (OR, 0.15; 95% CI, 0.46–0.50), compared with those with a CD4 lymphocyte count \geq 200 cells/ μ L (OR, 0.55; 95% CI, 0.31–0.99). The protective effect of vaccination with PPV was observed in all vaccinated patients independently of the time of vaccination, not only in those vaccinated \leq 5 years earlier (OR, 0.36; 95% CI, 0.17–0.77) but also in those vaccinated >5 years earlier (OR, 0.55; 95% CI, 0.34–0.98).

DISCUSSION

Although some studies have found a decrease in the incidence of pneumococcal disease in HIV-infected patients since the widespread use of HAART [3, 5, 9, 18], it remains one of the

Table 2. Microbiological data for HIV-infected patients with pneumococcal disease.

Test	Result
Sputum culture	42/94 (44.7)
Urinary antigen test	36/46 (78)
Blood culture	127/162 (78.4)
Pleural fluid culture	1/1
BAL culture	10/12
CSF culture	5/5
Ascitic fluid culture	4/4

NOTE. Data are expressed as no. of patients with positive result/no. of patients tested (%). BAL, bronchoalveolar lavage.

Table 3. Risk factors related to pneumococcal disease in HIV-infected adults.

Risk factor	Bivariate analysis		Multivariate analysis	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Male sex	1 (0.68–1.45)	1		
Smoking	0.84 (0.56–1.28)	.43		
Alcohol use	3.03 (1.86–4.91)	<.001	2.15 (1.11–4.19)	.02
Active injection drug use	3.33 (2–5.55)	.03		.46
CD4 lymphocyte count >200 cells/ μ L	1.04 (0.75–1.46)	.79		
HIV load <5000 copies/mL	0.38 (0.26–0.54)	<.001		.24
CDC HIV infection stage	0.85 (0.60–1.20)	.37		
TMP-SMZ use	0.66 (0.45–0.97)	.04		.80
Receipt of ART	0.23 (0.16–0.32)	<.001	0.23 (0.14–0.36)	<.001
HBV infection	0.71 (0.38–1.35)	.30		
HCV infection	1 (0.69–1.44)	1		
COPD	2.58 (1.3–5.1)	<.001	2.90 (1.21–6.94)	.02
Cirrhosis	6.05 (3.2–11.4)	<.001	5.64 (2.53–12.53)	<.001
Receipt of 23-valent PPV	0.39 (0.24–0.65)	<.001	0.44 (0.22–0.88)	.02

NOTE. ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus; HCV, hepatitis C virus; PPV, polysaccharide pneumococcal vaccine; TMP-SMZ, trimethoprim-sulfamethoxazole.

most common causes of hospital admission in these patients, and the incidence is higher among this group than among similarly aged individuals without HIV infection [1, 4–6, 10–12, 19]. This is especially true in patients with advanced HIV infection [3, 10].

It is worth noting that, despite actual recommendations regarding PPV vaccination, our study found that the rate of vaccination was low (~80% of our patients had not been vaccinated). This finding is in concordance with data documented by other authors, such as Dworkin et al. [7], who reported a vaccination rate in an American population of 37%, and Grau et al. [9], who reported an observed vaccination rate in a Spanish population of 7%–25%. In 1999, a pneumococcal vaccination program was begun in Spain, and within 18 months, vaccination coverage among the elderly population reached 35%, which is higher than that for HIV-infected patients [20].

The reasons for these low vaccination rates are probably related to the lack of evidence of the efficacy of the 23-valent PPV in HIV-infected patients, compared with the general population, including not only a lack of clinical efficacy but also a lower immunological response to vaccination in HIV-infected patients, compared with healthy control subjects, as has been demonstrated by other authors [21–25]. Another reason could be the belief that pneumococcal infection is not an important problem in HIV-infected patients in the developed world because of the widespread use of HAART and that it could be more cost-effective to concentrate efforts on strategies to improve adherence to antiretroviral therapy [18].

The most important conclusion in our study is that 23-valent PPV shows a significant, independent protective effect for pneumococcal disease in all HIV-infected patients, even in pa-

tients with CD4 lymphocyte counts <200 cells/ μ L. These results are in concordance with those observed in other cohorts [9, 25, 27] and case-control studies [7, 8, 13, 16]. However, in previous studies, this protection was limited to specific groups of patients, such as patients who were white [16] or those with CD4 lymphocyte counts \geq 200 cells/ μ L or \geq 500 cells/ μ L [7, 8, 13]. In our study, the protective effect of the 23-valent PPV in patients with CD4 lymphocyte counts <200 cells/ μ L, although showing a tendency to be stronger, is not statistically different from that observed in those with CD4 lymphocyte counts \geq 200 cells/ μ L. This is, to our knowledge, the first report to establish a stronger protective effect of PPV vaccination in patients with CD4 lymphocyte counts <200 cells/ μ L.

The main argument against the use of PPV comes from the only published randomized, double-blind, placebo-controlled trial, which involved HIV-infected patients from Uganda. This study demonstrated not only a lack of efficacy of the vaccine in preventing invasive pneumococcal disease, pneumococcal pneumonia, or death but also an increased risk of all-cause pneumonia in the group of vaccinated patients [17]. However, the results of this study would not be applicable in a developed country with full access to antiretroviral therapy; in our population, for example, 49% and 76% of case patients and control subjects, respectively, were receiving antiretroviral therapy.

The main objective of PPV vaccination should be to avoid pneumococcal infection. Recent data from hospitalized adults with pneumonia suggest that there are other objectives that could be achieved with PPV. In an observational study, Fisman et al. [26] found that prior pneumococcal vaccination was associated with a 40%–70% reduction in risk of in-hospital death in a large cohort of consecutive hospitalized individuals with

community-acquired pneumonia. The explanation for this phenomenon is that early death due to pneumococcal infection despite receipt of adequate antibiotic therapy may be caused by the release of cell wall components from killed pneumococci, which results in a cytokine-mediated inflammatory cascade that causes death [28]. It is possible that prior vaccination may contribute to preventing the development of such early inflammatory response and, consequently, may reduce early mortality and complications of pneumococcal infection. Although these data should be confirmed in future studies involving HIV-infected patients, they support the recommendation for pneumococcal vaccination.

Antiretroviral therapy demonstrated the strongest protective effect on pneumococcal infection in the multivariate analysis in our population. This result is in concordance with the findings of the majority of case-control [8, 11] and cohort studies [1, 3, 7].

Most other risk factors have been associated with pneumococcal disease in HIV-infected patients in previous reports, such as black race [7, 11, 19], smoking [1, 12], alcohol abuse [7, 9], injection drug use [7, 11], CD4 lymphocyte count <200 cells/ μ L [8, 11, 12], previous pneumonia or previous hospitalization [7–9], TMP-SMZ prophylaxis [1], or underlying conditions, such as lymphoma [12, 19], cirrhosis [9, 11, 12], COPD [12], or low albumin level [11]. In our study, only alcohol abuse and, in particular, comorbidities such as cirrhosis (OR, 5.64) and COPD (OR, 2.9) were important risk factors for pneumococcal disease.

Neither injection drug use nor TMP-SMZ prophylaxis reached a statistically significant level in the multivariate analysis of factors associated with pneumococcal disease in HIV-infected patients, although these risk factors were more frequent in case patients than in HIV-infected control subjects. Only Kohli et al. [1] found that TMP-SMZ prophylaxis was associated with a lower risk of bacterial pneumonia in a prospective cohort of women; this finding was in contrast with the findings of Jordano et al. [12], who not only did not find any protective effect against invasive pneumococcal disease, but also found that it was associated with increased rates of infection with TMP-SMZ-resistant and penicillin-resistant pneumococci.

The main limitation of our study is related to its retrospective design. Although we are aware of this limitation, we believe that our results are in concordance with those obtained in other geographical areas. As a consequence, some epidemiological data, such as data pertaining to smoking or alcohol abuse, which were collected retrospectively, may not be complete in clinical records. This could be the reason why smoking cigarettes was not a risk factor for pneumococcal disease, as was COPD, which is intimately associated with smoking cigarettes. Another limitation of our study is the fact that serotypes were not determined for pneumococcal isolates, and we could not

conclude whether case patients were infected with pneumococcal serotypes included in the 23-valent PPV.

A future randomized trial must answer some of the questions that remain as to the real effectiveness of the 23-valent PPV, the recommendation for revaccination every 5 years [24, 29], and the role that conjugate heptavalent pneumococcal vaccine will play. This vaccine is recommended for infants in the United States and in the majority of European countries, and its use has been associated with a reduction in incidence of invasive pneumococcal disease, not only in infants [30–32], but even in the elderly population [33] and among HIV-infected individuals [34]. Moreover, other strategies of sequential immunization with both the polysaccharide and the conjugate [35] vaccines should be explored. In the meantime, in our opinion, all HIV-infected patients must be vaccinated with the 23-valent PPV, even those with CD4 lymphocyte counts <200 cells/ μ L.

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