Pneumococcal Vaccination in HIV-Infected Adult Patients on Suppressive Antiretroviral Therapy, 2010-2017

M.J. Vivancos-Gallego (1), Alfonso Muriel (2), Sergio Serrano-Villar (1), Ana Moreno-Zamora (1), M.J. Pérez-Elías (1), Carmen Quereda (1), J.L. Casado (1), Matilde Sánchez-Conde (1), Santos Del Campo (1), Fernando Dronda (1), Carolina Gutierrez (1), Nadia Madrid (1), Ana M. Sánchez-Díaz (3), Jose Lorenzo Valencia-Martín (4), Santiago Moreno (1,5).

(1) Department of Infectious Diseases, University Hospital Ramon y Cajal and Ramón y Cajal Health Research Institute (IRYCIS), Madrid, Spain
(2) Clinical Biostatistics Unit, IRYCIS, University Hospital Ramón y Cajal, Madrid
(3) Microbiology Department, IRYCIS, University Hospital Ramón y Cajal, Madrid
(4) Preventive Medicine & Public Health Service, IRYCIS, University Hospital Ramón y Cajal, Madrid

BACKGROUND

There is little information on the effectiveness of the pneumococcal vaccines (PV), especially for the pneumococcal conjugate vaccines (PCVs), in HIV-infected patients in the modern antiretroviral era.
In HIV-infected patients, antiretroviral therapy (ART) has proven to be efficacious in reducing opportunistic and non-opportunistic events, including IPD (1). The benefit is higher when ART is initiated early in the course of HIV-infection (2). Several groups have recently reported the rates of and risk factors for IPD in HIV-infected adults on antiretroviral therapy (3,4). These authors have found that the rates of IPD remains higher than in the non-HIV infected population, and the IPD incidence in recent years (with an earlier ART initiation) has not been established. According to these studies, the real impact of systematic PV in an HIV-infected individual is questionable, and further studies are needed.
The goal of this study was to estimate the association of previous pneumococcal vaccination and IPD in HIV-infected patients in recent years, after adjusting for other *S. pneumoniae* disease risk factors. We compared HIV-infected patients with well documented IPD with matched HIV infected patients with no evidence of IPD in a case-control study.

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METHODS

STUDY DESIGN, SETTING, AND POPULATION

We performed a case-control study of HIV-infected adults attended at the Ramón y Cajal Hospital, a 1000-bed tertiary-care university hospital in Madrid providing care to more than 3000 HIV-infected patients. For the study, we retrospectively identified consecutive HIV-positive patients attending our clinic between January 2010 and December 2017. For the identification of HIV-infected patients with IPD, we used as a primary source the registries of the Department of Microbiology to identify all the patients with a positive sample for *S. pneumoniae* in the period.
Case Patients were defined as HIV-infected adults seen at the hospital in the period of study (from 1st January 2010 to 31st December 2017) with a well documented pneumococcal infection. In the case of pneumonia, a new lung consolidation with clinical pneumonia symptoms was required. Microbiological confirmation included isolation of *S. pneumoniae* from a normally sterile site (blood, cerebrospinal fluid, or joint fluid) and a positive urinary pneumococcal antigen.
Control Patients were selected by random sampling (3:1) of HIV infected patients without IPD, matched with case-patients only by gender and year of HIV-infection diagnosis.

During the study period, vaccination was prescribed according to the last updated version of the European AIDS Clinical Society Guidelines (EACS) and the Spanish Pneumococcal Immunization National Recommendations (1,2). Of note, recommendations for pneumococcal vaccination during the study changed. EACS guidelines recommended PPV23 between 2010-2013, but switched to PCV13 in 2014. Patients could have received only the PPV23 or both the conjugated and the PPV23. Depending on the time of vaccination, some individuals who had previously been vaccinated with the PPV23 received an additional PCV13 shot during the study. Patients included in the last years of the study were vaccinated following the current recommendations, consisting of the administration of PPV23 two months after PCV-13 (2). Vaccines prescribed in our area are registered in an official electronic vaccination record database. For purposes of analysis, we collected the date and type of vaccine (polysaccharide, conjugated or both) from this database, as well as the number of doses. We considered a patient as adequately vaccinated if PPV23 had been administered within the five previous years, or at any time after PCV7 or PCV13 administration.

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STATISTICAL ANALYSIS

To estimate the required samples size, a calculation was performed assuming a lower probability of vaccination among controls (0.50) than in cases (0.30), a power of 80%, alpha 5% and a 3:1 distribution. The sample size estimation was 184 controls and 61 cases (three matched controls by gender and year of HIV-infection diagnosis). Censoring was established at the IPD diagnosis for cases and last study visit for controls. Qualitative variables were reported as a frequency distribution, whereas quantitative variables were described as medians with their interquartile ranges (IQRs). Cross-sectional pairwise comparisons between groups were performed using the McNemar's test for categorical variables. Since, by definition, cases were not able to develop the outcome before receiving the PV, to account for immortal time bias, we defined PV exposure as a time-dependent covariate in the Cox proportional-hazards regression model. We considered all included individuals at risk for the outcome since the beginning of the period of study (January 2010 or date of HIV diagnosis if it was done after January 2010). Statistical analyses were performed using Stata v15.0 (StataCorp LP, College Station, TX).

RESULTS

POPULATION OF STUDY

According to the records of the Microbiology Department, IPD was diagnosed in 901 patients in the period from January 2010 through December 2017. Among these, 72 (8%) patients were HIV-infected, after crossmatching with the registry of HIV-infection in the hospital (n = 3152). Eight patients were excluded from analysis due to missing information. Thus, cases included 64 HIV-infected patients with microbiologically confirmed IPD. After random selection matching, controls were 192 HIV-infected subjects matched with cases by gender and year of HIV-infection diagnosis (3:1).

DESCRIPTION OF CASES

Among the 64 cases of IPD, there were 46 episodes of pneumonia (71.9%, nine of these with bacteremia), 17 episodes of bacteremia (26.5%), and one episode of joint infection (1.6%).

TABLE 1. Baseline characteristics of cases and control patients. Univariate analysis of risk factors associated with IPD.

Variable/Factor	Cases (n = 64)	Controls (n = 192)	P
Age at HIV-diagnosis (years), median (IQR)	30 (25-37)	29 (24-36)	.864
Observation time (months), median (IQR)	36 (10-67)	95 (95-95)	.0001
Male sex, n (%)	49 (77%)	146 (76%)	1.000
Risk factor for HIV, n (%)	64 (100)	192 (100)	.0001
Intravenous drug use, n (%)	52 (83%)	78 (40%)	
MSM	4 (6%)	64 (34%)	
Heterosexual	6 (10%)	46 (24%)	
Others	2 (1%)	4 (2%)	
Previous AIDS, n (%)	47 (76%)	64 (36%)	.0001
Nadir CD4 cell count (cells/ml), median (IQR)	74 (26-144)	177 (96-314)	.0001
Nadir CD4 cell count <200 cells/ml, n (%)	18 (31%)	21 (11%)	.0001
CD4/CD8 ratio, median (IQR)	0.3 (0.2-0.6)	0.7 (0.4-1)	.0001
On ART, n (%)	49 (76.6)	178 (92.7)	.0001
Time to ART initiation (months), median (IQR)	53 (7-121)	13 (2-73)	.007
Time on ART (years), median (IQR)	15 (6-21)	19 (9-22)	.314
HIV RNA<1.57 log, n (%)	36 (60%)	166 (87%)	.0001
Diabetes, n (%)	2 (3%)	13 (7%)	.372
Cancer, n (%)	4 (7%)	9 (5%)	.529
Cardiovascular disease, n (%)	11 (28%)	29 (15%)	.690
Cirrhosis, n (%)	32 (52%)	34 (18%)	.0001
Chronic Pulmonary Disease, n (%)	27 (44%)	29 (15%)	.0001
Chronic Renal Failure, n (%)	6 (10%)	7 (4%)	.093
Charlson Comorbidity Index, median (IQR)	6 (2-8)	1 (1-3)	.0001
Pneumococcal vaccination, n (%)	21 (33%)	94 (49%)	.041

Of the 64 patients with IPD, 60 (93.7%) had been hospitalized in the Infectious Diseases Department, including 13 patients who required intensive care at some time during their admission. All-cause mortality was high (30%), with death being directly attributable to *S. pneumoniae* infection in eight cases (12.5% of all cases).

PNEUMOCOCCAL VACCINATION

TABLE 2. Characteristics of HIV-infected patients according to vaccination status

Variable/Factor	Vaccinated (n = 115)	Non-vaccinated (n = 141)	P
CD4 cell count (cells/ml), median (IQR)	561 (347-760)	487 (241-725)	.054
Age at HIV-diagnosis (years), median (IQR)	29 (24-36)	30 (25-36)	.526
Follow-up (months), median (IQR)	46.3 (23.7-97.4)	97 (59.3-97.4)	0.00001
Male sex, n (%)	87 (75.7)	108 (76.6)	.86
Risk factor for HIV, n (%)	115 (100)	141 (100)	.264
Intravenous drug use, n (%)	55 (47.8)	75 (53.2)	
MSM	31 (26.9)	37 (26.2)	
Heterosexual	28 (24.3)	24 (17)	
Others	1 (0.9)	5 (3.6)	
Previous AIDS, n (%)	40 (34.8)	71 (50.3)	.007
Nadir CD4 cell count (cells/ml), median (IQR)	179 (71-314)	127 (51-229)	.014
Nadir CD4 cell count <200 cells/ml, n (%)	10 (8.7)	29 (20.6)	.005
CD4/CD8 ratio, median (IQR)	0.6 (0.4-1.1)	0.5 (0.3-0.8)	.047
On ART, n (%)	104 (90.4)	123 (87.2)	.896
Time to ART initiation (months), median (IQR)	13 (2-67)	36 (3-96)	.160
Time on ART (years), median (IQR)	19 (10-23)	17 (7-21)	.006
HIV RNA <1.57 log cop/mL, n (%)	99 (86)	103 (73)	.040
Diabetes, n (%)	10 (8.7)	5 (3.5)	.340
Cancer, n (%)	5 (4.3)	8 (5.7)	.635
Cardiovascular disease, n (%)	20 (17.4)	20 (14.2)	.546
Cirrhosis, n (%)	29 (25.2)	37 (26.2)	.800
Chronic Pulmonary Disease, n (%)	28 (24.3)	28 (19.9)	.440
Chronic Renal Failure, n (%)	5 (4.3)	8 (5.7)	.612
Charlson Comorbidity Index, median (IQR)	1 (1-4)	1 (1-4)	.527
Invasive Pneumococcal Disease, n (%)	21 (19)	43 (30)	.025
Bacteraemia, n (%)	7 (6)	10 (7)	.906

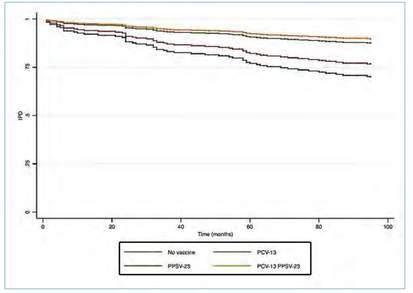


FIGURE 1. Unadjusted cumulative hazard function plot for the risk of invasive pneumococcal disease by immunization groups. PCV13 or PCV7 HR 0.75 (95%, CI 0.3–1.9); PPV23 HR 0.38 (95%, CI 0.1–1.05); PPV23-PCV13 HR 0.31 (95%, CI 0.1–0.8) p =0.012. Reference: unvaccinated.

TABLE 3. Schedules of administration of the pneumococcal vaccines to 115 HIV-infected patients

Immunization Schedules	Total (115/256)	Cases (21/64)	Controls (94/192)	The median time between vaccines (IQR)
Only PPV23	30	8	22	NA
Only PCV13	20	5	15	NA
Only PCV7	2	0	2	NA
PPV23 - PPV23	8	1	7	3.5 (2-5) years
PCV13 - PPV23	20	0	20	2 (1-2) months
PPV23 - PCV13	35	7	28	5 (4-6) years

MULTIVARIATE ANALYSIS OF RISK FACTORS FOR IPD IN HIV-INFECTED PATIENTS

TABLE 4. Multivariate Cox Regression Analysis for risk factors associated with IPD in HIV-infected patients.

Immunization Schedules	Adjusted hazard ratio* (95% confidence interval)	P
Only PPV23 (including PPV23-PPV23)	0.58 (0.21-1.64)	0.305
Only PCV7 or PCV13	0.76 (0.29-1.95)	0.569
PCV13-PPV23 or PPV23-PCV13	0.42 (0.15-1.19)	0.102

TABLE 5. Multivariate Cox Regression Analysis for protection against IPD according to immunization schedules in HIV-infected patients.

Variable	Adjusted hazard ratio (95% confidence interval)	P
Pneumococcal vaccination	0.68 (0.35-1.32)	.250
CD4nadir	0.99 (0.98-0.99)	.001
Charlson Comorbidity Index*	1.16 (1.06-1.27)	.001
Cirrhosis	1.71 (0.89-3.30)	.11
Plasma HIV RNA < 1.57 log	0.52 (0.27-1.02)	.06

*excluding AIDS

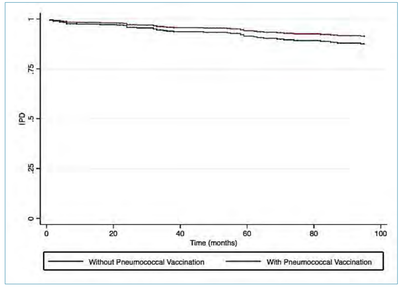


FIGURE 2. Adjusted cumulative hazard function plot for the risk of invasive pneumococcal disease in vaccinated patients, HR 0.65 (95% CI 0.35–1.32) P = 0.250. Adjusted for HIV RNA<1.57 log copies/mL, CD4 nadir, Charlson index and cirrhosis

DISCUSION

In this case-control study, we could not demonstrate a protective effect of PV against IPD in HIV-infected patients. The development of IPD appeared to be more related to comorbidities and traditional risk factors for *S. pneumoniae* infection, as in the HIV-uninfected population, than with the vaccine itself. The finding is supported by the fact that the vaccine was administered to patients who could experience the greatest benefits, with most of them (90%) being on ART, with a high CD4 count (median 561 cells/ml), and undetectable plasma viral load in the majority of patients (86% had < 50 HIV RNA copies/mL) (Table 2). Moreover, the coverage rates in our population were relatively high (44%) compared to other studies (1), and PCV-13 vaccine was used in more than 50% of the patients.

Randomized clinical trials have demonstrated differential effects of PCV and PPV on IPD in HIV-infected adults. French et al. demonstrated no efficacy in reducing the risk of pneumococcal disease among Ugandan HIV-positive persons not taking ART (2). Later, a placebo-controlled, double-blind clinical trial with PCV-7 performed in Malawi among patients mostly not using ART showed a reduction of 74% in IPD caused by serotypes included in the vaccine (3). In the study, only half of the episodes in the placebo recipients were caused by vaccine serotypes and serotype 6A. However, serotype coverage was improved with the development of a PCV13 (4). Since higher immunogenicity has been reported with the administration of PCV13 followed by a dose of PPV23 (5), a prime-boost strategy has been proposed to optimize the response (6). Nevertheless, no previous experience with PCV13, alone or followed by PPV23, has been reported in HIV-patients.

In our study, the overall results did not show protection from the vaccine. However, more than half of the vaccinated patients had received a single dose of the vaccine (mostly PPV23 or PCV13) or had received a double dose of only PPV23. Since these are not included among the currently recommended schedules of administration, we examined the effect of a boosting strategy that included a conjugate vaccine. After adjusting for relevant variables, the lack of an association was confirmed. Moreover, the currently recommended strategy of combining a prime with a PCV followed by a boost with PPV23 4 to 8 weeks apart, was administered to 20 patients with no episodes of IPD developing among them. It must be emphasized that this observation is limited to a small number of patients with the shortest follow-up and distinct characteristics (few comorbidities, low modified Charlson index).

Consistent with prior studies, risk factors for IPD rely on comorbidities, lower CD4 count or AIDS-defining conditions, and, to a lesser extent, in plasma viral load (7). Our population of the study had a high number of comorbidities known to increase the risk of IPD. We identified these comorbidities as the risk factors more strongly associated with IPD, as reflected by the modified Charlson comorbidity index, above the HIV-related factors that were also associated (CD4 nadir).

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LIMITATIONS

- This is an observational, case-control study and, therefore, our findings must be interpreted with caution given the potential biases. Although we tried to collect all potential risk factors for IPD and the multivariate analyses controlled for most of them, other potentially relevant factors might have been missed. A selection bias cannot be ruled out.
- The study was retrospective and covered a period of 8 years, in which different types of vaccines and schedules of immunization were used, which may have somewhat overestimated the risk of the case event and underestimated efficacy of the vaccines in the first years of the study.
- PCV effectiveness depends on serotype distribution in a carriage during PCV implementation, and we were not able to retrieve data for pneumococcal serotypes, nor do we have information on the serotypes of the isolates in our patients.
- The study only includes HIV individuals with IPD admitted to the hospital, which might have underestimated the number of case-patients.
- The exposure to children in household who may have received PCV will also represent an important source of uncontrolled confounding.
- We acknowledge the limitations of the study and the need of new studies looking at the impact of currently recommended vaccination schedules (PCV13 alone or PCV13 + PPV23) on bacteraemic or non-bacteraemic pneumonia in HIV-infected persons, which would require substantially larger samples size in the context of a multi-centre study.

CONCLUSIONS

In this case-control study, we could not show an association between PV and IPD, although a protective effect of particular schedules of immunization cannot be ruled out. The sample size was probably small to observe statistical differences in the outcome but trended in the direction of a beneficial vaccine effect in reducing IPD in high risk HIV individuals, as some traditional factors and comorbidities could explain most of the risk.

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