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Pneumonia in HIV-Infected Patients in the HAART Era: Incidence, Risk, and Impact of the Pneumococcal Vaccination

C. López-Palomo,[1] M. Martín-Zamorano,[1] E. Benítez,[2] C. Fernández-Gutiérrez,[3] F. Guerrero,[1] M. Rodríguez-Iglesias,[4] and J.A. Girón-González[1]*

[1]*Internal Medicine, Hospital Universitario Puerta del Mar, Facultad de Medicina, Cádiz, Spain*
[2]*Epidemiology, Hospital Universitario Puerta del Mar, Facultad de Medicina, Cádiz, Spain*
[3]*Microbiology Services, Hospital Universitario Puerta del Mar, Facultad de Medicina, Cádiz, Spain*
[4]*Microbiology Service, Hospital Universitario Puerto Real, Cádiz, Spain*

The objective of this study was to assess the factors implicated in an increased or decreased risk of pneumonia, with particular attention to the response to highly active antiretroviral therapy (HAART) and the effect of the polysaccharide 23-valent pneumococcal vaccination in 300 human immunodeficiency virus (HIV)-infected adults followed-up for a median of 35.6 months. Pneumococcal pneumonia occurred in 12 patients and all bacterial pneumonia (pneumonia caused by *Streptococcus pneumoniae* or other bacteria, as well as those with negative cultures but presumably bacterial in origin) in 40 patients. In the univariate analysis, immunodepressed patients (defined as those with less than 200 CD4+ T cell/μl), those without immunological response to HAART (defined as an increase of 25% of CD4+ T lymphocyte count), patients with previous admissions to hospital and those with cotrimoxazole or *Mycobacterium avium intracellulare* prophylaxis showed a higher incidence of both pneumococcal and all bacterial pneumonia. Multivariate analysis demonstrated that the presence of pneumococcal pneumonia was associated with a CD4+ lymphocyte count at the time of HIV diagnosis <200 cells/μl. The multivariate model that was more valid for prediction of all bacterial pneumonia included a CD4+ T cell count <200 cells/μl and absence of immunological response to HAART. Only in patients with a baseline CD4+ T cell count lower than 200/μl and immunological response to HAART, a near significant lower incidence of all bacterial pneumonia was observed after vaccination. Thus, these results do not support an important additional protective effect of 23-valent pneumococcal vaccine in HIV-patients with immunological response to HAART. ***J. Med. Virol. 72:517–524, 2004.*** © 2004 Wiley-Liss, Inc.

KEY WORDS: pneumococcal disease; highly active antiretroviral therapy; vaccination; HIV infection; pneumonia; bacteremia

INTRODUCTION

Infection with *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia among persons infected with the human immunodeficiency virus (HIV) [Centers for Disease Control and Prevention, 1997]. Antibodies to capsular polysaccharides confer protective immunity to *S. pneumoniae*, and this is the basis for the use of the currently licensed 23-valent pneumococcal polysaccharide vaccine. This vaccine prevents invasive pneumococcal disease caused by vaccine serotypes among immunocompetent persons [Centers for Disease Control and Prevention, 1997]; its effectiveness in preventing invasive disease among immunosuppressed persons, such as those infected by HIV, is less clear [Lindenburg et al., 2001]. Therefore, a case-control study conducted by Gebo et al. [1996] suggested an effectiveness of 78% for prevention of pneumococcal bacteremia among HIV-infected patients with CD4+ cell counts greater than 200 cells/μl, but did not find effectiveness among persons with lower CD4+ cell counts. These findings were supported later by other researchers [Breiman et al., 2000; Dworkin et al., 2001]. In contrast, a recent prospective, randomized, placebo-controlled study conducted in Uganda found no effect in

*Correspondence to: J.A. Girón-González, Servicio de Medicina Interna, Hospital Universitario Puerta del Mar, avda. Ana de Viya 21, 11009 Cadiz, Spain. E-mail: joseantonio.giron@uca.es.

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preventing invasive pneumococcal disease or pneumonia [French et al., 2000]. However, no investigation that estimated pneumococcal vaccine effectiveness among HIV-infected patients has been conducted among patients who have benefited from highly active antiretroviral therapy (HAART).

To provide information useful on pneumococcal vaccine use in the HAART era, we conducted the present study of the effectiveness of the 23-valent pneumococcal polysaccharide vaccine among HIV-infected adults.

MATERIALS AND METHODS

The aim of this study was to assess the factors implicated in an increased or decreased risk of pneumonia, with particular attention to the response to HAART and the effect of the polysaccharide 23-valent pneumococcal vaccination. A cohort of 300 HIV-infected patients has been followed-up at a single university hospital in Cadiz, Spain, from January 1997 to December 2000. This tertiary center serves a population of 270,000 inhabitants. Cumulative prevalence of acquired immunodeficiency syndrome (AIDS) in our area is 570 per million of inhabitants.

Members of the staff abstract data from the medical records of HIV-infected patients, including demographic data (age, sex, drug-use habits including alcoholism), hospitalization that occurred during the previous 6-month period, HIV infection-related data (risk factor for HIV infection, CD4+ T lymphocyte count, opportunistic diseases, *Pneumocystis carinii* prophylaxis with trimethoprim-sulfamethoxazole, *Mycobacterium avium complex* prophylaxis with clarithromycin or azitromycin, antiretroviral therapy (HAART), and immunological response to it), symptoms and signs of pneumonia, and pneumococcal vaccination status. The initial data abstraction is followed by abstraction that was undertaken every 6 months until the patient either dies or is lost to follow-up. Data reflect follow-up observations that occurred from January 1997 to December 2000.

The study protocol was approved by the Institutional Ethical Committee and all patients and controls gave their informed consent.

Definitions

Patients were considered as having a pneumonia if they met the following three criteria: (1) presence of fever (temperature $>38^{\circ}$C), dyspnea, cough, and/or expectoration; (2) a new pulmonary infiltrate in a chest radiograph, for which noninfectious causes were excluded; and either (3a) a diagnosis based on at least one of the following samples: blood, pleural fluid, sputum with culture, bronchial aspirate ($\geq 10^6$ cfu/ml), bronchoalveolar lavage fluid ($\geq 10^4$ cfu/ml), protected brush specimen ($\geq 10^3$ cfu/ml), transbronchial biopsy or pulmonary needle aspirate; or (3b) the presence of the first two criteria and a cure with antibacterial treatment (other than cotrimoxazole) [Cordero et al., 2000]. A bacterial species was considered to have caused pneumonia when it was isolated as a single pathogen in sterile fluids, or when it was the only organism isolated from respiratory samples [Cordero et al., 2002].

Pneumococcal pneumonia was defined as physician-diagnosed pneumonia, bacteremia or pleuritis, for which *S. pneumoniae* was identified as the etiological agent. Diagnoses of pneumococcal otitis, sinusitis, or bronchitis were not recorded because these clinical conditions can be viral in patients with pneumococcal carriage.

S. pneumoniae was identified on the basis of typical colonial morphology on Mueller–Hinton agar with 5% defibrinated horse blood, characteristic findings of gram staining, results of disk diffusion tests with optochin, bile solubility, and results of latex agglutination tests.

"All bacterial pneumonias" was the term used to encompass cases of all etiologies, including those caused by *S. pneumoniae*, those caused by other identified bacteria, and those with negative cultures but presumably bacterial in origin.

Indications for HAART were based on individual clinical, immunologic, and virologic status according to the periodic "Recommendations of the International AIDS Society" [Carpenter et al., 1996, 1997, 1998, 2000]. Treatment with two nucleoside analogues and a protease inhibitor or a non-nucleoside analogue was indicated to each of the patients included in this protocol. In order to classify the types of response to HAART, three categories were established: (1) group 1: patients with more than 200 CD4+ T cells/μl at inclusion and an increase higher than 25% of CD4+ T lymphocyte count after treatment, maintained for at least 6 months. An additional group of eight patients presented with more than 200 CD4+ T cells/μl at inclusion; although the CD4+ T lymphocyte count increase was lower than 25%, they maintained a count higher than 200/μl at the end of follow-up and they are considered conjointly with the first group. (2) group 2: patients with less than 200 CD4+ T cells/μl at inclusion and an increase of 25% of CD4+ T lymphocyte count after treatment, maintained for at least 6 months; CD4+ T cell count was higher than 200/μl at the end of follow-up. (3) group 3: patients with less than 200 CD4+ T cells/μl at inclusion and not attaining more than 200/μl at the end of follow-up.

Determination of the Vaccination Status

Pneumococcal vaccine (Pneumovax, Pasteur, Paris, France) was provided by the members of the Infectious Unit of the Internal Medicine Service. Vaccination status and date of vaccination are recorded systematically in the clinical chart of every patient.

Statistical Analysis

Unless otherwise indicated, data are presented as mean ± standard deviation or as absolute number and percentage. Qualitative variables were compared using the x^2 or Fisher's exact test. Quantitative variables were compared using the Student's *t*-test or analysis of variance. The relation of covariates with pneumococcal

pneumonia or all bacterial pneumonias was assessed by univariate analysis.

Those factors that were associated with risk in the univariate analysis with a *P*-value of less than 0.10 or were potential confounders based on previous studies were included in the multivariate models via logistic regression. Vaccination status was the independent variable included in all models and pneumococcal pneumonia or all bacterial pneumonias the dependent variables. We used stepwise (backward) elimination to determine variables that were independent predictors. A *P*-value lower than 0.05 was considered significant.

RESULTS

Baseline Characteristics

Of 300 HIV-1-infected patients studied, 159 had received 23-valent pneumococcal polysaccharide vaccine and 141 had not been vaccinated with it. Baseline characteristics of patients, according to their vaccination status, are presented in Table I. Median CD4+ T cell/μl count at vaccination was 315 (95% CI: 32–901); 50 patients (31.4%) had a CD4+ T cell/μl at vaccination lower than 200. Prior to their inclusion in the study, the patients had been receiving HAART during at least 6 months (vaccinated group: median 6.5 months, range 6–9 months; unvaccinated group: 7.3 months, range 6–9 months, $P > 0.05$).

Follow-Up

Median follow-up period of the patients was 35.6 months (range 2–60). A virological response to HAART (viral load <50 copies/ml) was present in 168 (56%) out of 300 patients. Mean increase of CD4+ lymphocyte count from the beginning of the HAART until the end of the follow-up was 138 ± 122 cells/μl. In function of the response to HAART, patients were classified in three groups (see above "Materials and Methods"): group 1, 140 patients (46.7%); group 2, 56 patients (18.7%); and group 3, 104 individuals (34.7%).

Forty cases of community-acquired pneumonia were diagnosed. The etiology of community-acquired pneumonia was: *S. pneumoniae* 12 cases (30%), *Haemophilus influenzae* 2 cases (5.0%), *Pseudomonas aeruginosa* 2 cases (5.0%), *Klebsiella pneumoniae* 1 case (2.5%), and unknown cause 23 cases (57.5%). Table II gives a breakdown of total pneumonia cases by etiology and vaccination status. The CD4+ T lymphocyte count, obtained within 3 months of the diagnosis of pneumonia, of these patients was 196 ± 193 (range 10–751) cells/μl.

In vaccinated patients, pneumococcal pneumonia presented after 16.3 ± 15.4 (range: 6–34) months after the vaccination and community-acquired pneumonia after 28.6 ± 17.5 (range: 4–60) months.

Differences between groups 1 and 2 (groups with more than 200 CD4+ T cell/μl at the end of follow-up) with respect to the incidence of pneumococcal pneumonia (3 cases—2.1% of group 1 and 1 case—1.8% of group 2) and all bacterial pneumonias (12 cases—8.6% and 6 cases—10.7%) were not significant; these two groups will be considered jointly from here on. In contrast, significantly higher incidences of pneumococcal (8 cases—7.7%) ($P = 0.014$) and all bacterial (22 cases–19.2%) ($P < 0.001$) pneumonias occurred in patients of group 3 (patients with less than 200 CD4+ T cells/μl during the follow-up).

Parameters Associated With an Increased Incidence of Pneumonia

We examined the influence of several factors, indicated in Table III, on the presence of pneumonia. Immunodepressed patients (defined as those with less than 200 CD4+ T cells/μl), those without attaining more than 200 CD4+ T cells/μl after HAART, patients with previous admissions to hospital and those with cotrimoxazole or *Mycobacterium avium intracellulare* prophylaxis all showed a higher incidence of both pneumococcal and all bacterial pneumonias. Incidence of pneumococcal pneumonia was less frequent in vaccinated patients, the difference approaching statistical significance ($P = 0.073$). Significant lower incidence of all bacterial pneumonias was observed in vaccinated patients (Table III).

TABLE I. Baseline Characteristics of Patients, According to Their Vaccination Status

Variable	Total patients (n = 300)	Vaccinated patients (n = 159)	Unvaccinated patients (n = 141)
Males/females ratio	1.3:1	1.3:1	1.2:1
Age (mean ± SD), year	37 ± 7	37 ± 7	37 ± 7
Drug users, n (%)	205 (68.3)	109 (68.6)	96 (68.1)
Current smoker, n (%)	275 (91.7)	144 (90.6)	131 (92.9)
Ethanol ingestion >50 g/day, n (%)	90 (30.0)	51 (32.1)	39 (27.7)
Admitted to hospital during previous period of 6-months, n (%)	40 (13.3)	24 (15.3)	16 (11.1)
Minimal CD4+ cell count (mean ± SD), cells/μl	327 ± 236	343 ± 241	309 ± 209
Maximal HIV viral load (mean ± SD), copies/ml ×1,000	128 ± 337	115 ± 417	146 ± 245
Cotrimoxazole prophylaxis, n (%)	113 (37.6)	54 (34.0)	59 (41.8)
Mycobacterium avium intracellulare prophylaxis, n (%)	73 (24.3)	37 (23.3)	36 (25.5)

TABLE II. Types of Infection, According to Their Vaccination Status

Variable	Total patients (n = 300)	Vaccinated patients (n = 159)	Unvaccinated patients (n = 141)	Odds ratio (OR) (95% CI)	*P*
Pneumococcal pneumonia, n* (%)	12 (4.0)	3 (1.9)	9 (6.4)	0.232 (0.075–1.063)	0.073
Pneumococcal bacteremia, n* (%)	7 (2.3)	1 (0.6)	6 (4.3)	0.142 (0.017–1.198)	0.054
Community acquired pneumonia, unknown causes, n* (%)	23 (7.7)	10 (6.3)	13 (9.1)	0.564 (0.245–1.299)	0.211
Community acquired pneumonia, all etiologies, n* (%)	40 (13.3)	14 (8.8)	26 (18.4)	0.427 (0.213–0.855)	0.017

n*, represents number of patients with infection.

An additional analysis was carried out to detect the efficacy of vaccination on pneumococcal and all bacterial pneumonias when the CD4+ T cell count was higher or lower than 200 cells/μl, as well as when an immunological response to HAART prior to vaccination was detected or not. Only in those patients with a CD4+ T cell count lower than 200/μl at inclusion and immunological response to HAART attaining more than this value, the incidence of all bacterial pneumonias was lower (at close to significance) in vaccinated patients (Fig. 1).

Multivariate Analysis

Next, the importance of age, gender, risk factor for HIV infection, ethanol or tobacco use, admissions to hospital during previous 6-month period, minimal CD4+ T lymphocyte count, maximal HIV viral load, response to HAART, cotrimoxazole or *Mycobacterium avium intracellulare* prophylaxis and pneumococcal vaccination on pneumococcal and all bacterial pneumonias were studied. The presence of pneumococcal pneumonia was associated with a CD4+ lymphocyte count at HIV diagnosis <200 cells/μl. The multivariate model which was more valid for prediction of all bacterial pneumonias included a CD4+ T cell count <200 cells/μl and absence of a sufficient immunological response to HAART (a CD4+ T cell count persistently lower than 200 cells/μl during the follow-up) Table IV.

DISCUSSION

Examination of those factors which could be associated with a higher incidence of pneumonia in HIV-infected patients was carried out. The incidence of pneumonia in our patients is similar to that observed in two previous studies of our group in this area [Clavo-Sanchez et al., 1997; Cordero et al., 2000]. Likewise, this incidence is similar to that of other studies analyzing this topic [Dworkin et al., 2001].

Univariate analysis demonstrated that the incidence of pneumococcal and all bacterial pneumonias was significantly higher in HIV-infected patients with a low CD4+ T cell count, as has previously been reported [Schuchat et al., 1991; Gebo et al., 1996; Dworkin et al., 2001]. The higher incidence in those patients on cotrimoxazole or *Mycobacterium avium intracellulare* prophylaxis is probably related to the fact that these treatments are administered to the more immunodepressed patients. Also, our study and those of other authors [Fedson and Chiarello, 1983; Hirschtick et al., 1995; Havlir et al., 1996; Dworkin et al., 2001] have found that this incidence was higher in patients with previous admissions to hospital. However, we have been not able to confirm previous studies that have found increases in pneumonia in individuals with tobacco or alcohol abuse or parenteral drug use [Gebo et al., 1996; Guerrero et al., 1999; Dworkin et al., 2001].

Although the use of HAART has been associated with decreased rates of pneumonia and bacteriemia in patients with advanced HIV infection, who are at greatest risk of invasive pneumococcal infections [Tacconelli et al., 1998; Paul et al., 1999; Pierce and Hoy, 2001], the relation between an immunological response to HAART and the incidence of pneumonia has not previously been analyzed. Consequently, we believe that the most interesting finding of our study is the demonstration that the factor influencing the incidence of bacterial pneumonia in these individuals, in addition to a CD4+ T cell count lower than 200/μl, was the immunological response to HAART. Effectively, the risk of bacterial pneumonia was reduced by half in patients who attain and/or maintain a CD4+ T cell count higher than 200/μl after HAART. Taking into account the effect of immunological status and the response to HAART, the other factors related to higher incidences of pneumococcal and all bacterial pneumonias lose their statistical significance. Similar features have been demonstrated for the incidence of other opportunistic infections in HIV-infected patients: when CD4+ T cell count and immunological response to HAART is considered, the relative risk of these events dramatically decreases [Palella et al., 1998; McNahten et al., 1999]. Thus, our data on pneumonia add more proof to the efficacy of HAART in the reduction of opportunistic infections in HIV-infected patients.

Further, this study provides additional information on the efficacy of the 23-valent pneumococcal vaccine. Administration of pneumococcal vaccine to HIV-infected patients is supported by several factors (it is inexpensive [Rose et al., 1993], it covers the majority of pneumococcal serogroups that cause pneumococcal bacteremia [Bartlett, 1998], and their adverse effects are negligible [Kroon et al., 1996; Santos et al., 2002]). However, contradictory results on the efficacy of 23-valent pneumococcal pneumonia in HIV-infected patients have been reported previously [Gebo et al.,

TABLE III. Risk Factors for Pneumococcal and all Bacterial Pneumonia in HIV-Infected Patients

Variable	Pneumococcal pneumonia (n = 12)			All bacterial pneumonia (n = 40)		
	n (%)	OR (95% CI)	*P*	n (%)	OR (95% CI)	*P*
Gender						
Male (n = 215) vs. female (n = 85)	7 (3.3) vs. 5 (5.9)	0.54 (0.15–2.02)	0.331	30 (14.0) vs. 10 (11.8)	1.22 (0.54–2.81)	0.753
HIV risk factor (n, %)						
Drug users (n = 205) vs. others (n = 95)	9 (4.4) vs. 3 (3.2)	1.41 (0.34–6.73)	0.758	30 (14.6) vs. 10 (10.5)	1.46 (0.65–3.35)	0.429
Current smoker (n, %)						
Yes (n = 275) vs. no (n = 25)	11 (4.0) vs. 1 (4.0)	1.00 (0.12–21.58)	1.000	37 (13.5) vs. 3 (12.0)	1.14 (0.30–5.05)	1.000
Ethanol ingestion >50 g/day, n (%)						
Yes (n = 90) vs. no (n = 210)	3 (3.3) vs. 9 (4.3)	0.77 (0.16–3.20)	1.000	10 (11.1) vs. 30 (14.2)	0.75 (0.33–1.69)	0.578
Admission to hospital during previous 6-month						
Yes (n = 40) vs. no (n = 260)	10 (25.0) vs. 2 (0.8)	43.00 (9.00–205.56)	0.000	25 (62.5) vs. 15 (5.8)	27.22 (11.92–62.15)	0.000
Maximal HIV viral load (copies/ml)						
>50,000 (n = 152) vs. <50,000 (n = 148)	6 (3.9) vs. 6 (4.0)	0.97 (0.27–3.50)	0.805	17 (11.1) vs. 23 (15.5)	0.68 (0.33–1.41)	0.347
Minimal CD4+ T cell/μl						
<200 (n = 122) vs. ≥200 (n = 178)	9 (7.4) vs. 3 (1.7)	4.65 (1.12–22.50)	0.030	26 (21.3) vs. 14 (7.9)	3.17 (1.50–6.75)	0.001
CD4+ T cell count ≥200/μl at the end of follow-up (immune response to HAART)						
Yes (n = 196) vs. no (n = 104)	4 (2.3) vs. 8 (7.7)	0.25 (0.06–0.94)	0.027	20 (10.2) vs. 20 (19.2)	0.48 (0.23–0.98)	0.044
Pneumococcal vaccine (%)						
Yes (n = 157) vs. no (n = 143)	3 (1.9) vs. 9 (6.4)	0.282 (0.075–1.063)	0.073	14 (8.8) vs. 26 (18.4)	0.427 (0.213–0.855)	0.017
Cotrimoxazol prophylaxis (%)						
Yes (n = 113) vs. no (n = 187)	8 (7.1) vs. 4 (2.1)	3.49 (0.92–14.13)	0.063	23 (20.4) vs. 17 (9.1)	2.56 (1.24–5.31)	0.004
Mycobacterium avium intracellulare prophylaxis (%)						
Yes (n = 73) vs. no (n = 227)	7 (9.6) vs. 5 (2.2)	4.73 (1.29–17.85)	0.010	18 (24.7) vs. 19 (9.3)	3.58 (1.66–7.72)	0.001

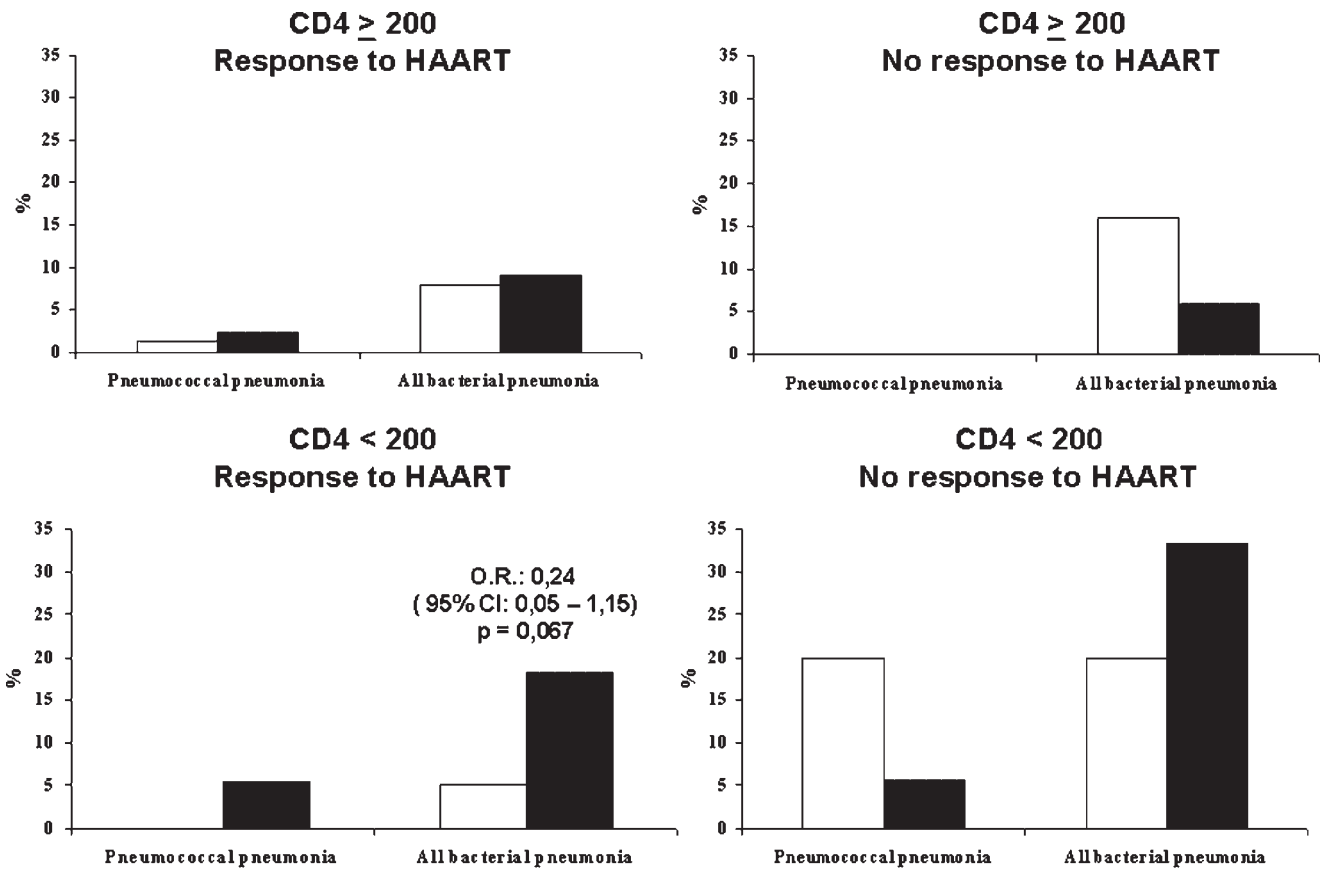

Fig. 1. Percentages of patients with pneumococcal and all bacterial pneumonia, distributed in function of the minimum CD4+ T cell count, the response or absence of response to highly active antiretroviral therapy (HAART) treatment and the pneumococcal vaccination (vaccinated patients (□), unvaccinated patients (■).

1996; Breiman et al., 2000; French et al., 2000; Dworkin et al., 2001]. Thus, whereas some researchers did not detect any significant effect on the pneumococcal disease [French et al., 2000], others recommended the vaccination in those HIV-infected patients with counts of more than 200 [Gebo et al., 1996; Breiman et al., 2000] or more than 500 CD4/μl [Dworkin et al., 2001]. In our study, vaccination was associated with a near-significantly lower incidence of pneumococcal pneumonia and a significantly lower incidence of all bacterial pneumonias in the univariate analysis; however, we did not detect a definite protective effect of the vaccination in the multivariate analysis. Several explanations could be operative: (1) this was an observational study and

TABLE IV. Multivariate Analysis of Parameters Implicated in Pneumococcal and all Bacterial Pneumonia

					IC95% Exp (B)	
Variable	β	Wald	*P*	Exp (B)	Minimum	Maximum
Pneumococcal pneumonia						
CD4+ T cell count <200/μl at inclusion	1.612	3.953	0.047	5.012	1.023	24.552
−2 Log likelihood: 75.725						
Chi-squared: 4.875						
$P = 0.027$						
All bacterial pneumonia						
CD4+ T cell count <200/μl at inclusion	0.678	3.394	0.065	1.971	0.958	4.056
CD4+ T cell count ≥200/μl at the end of follow-up (immune response to HAART)	−0.732	3.624	0.057	0.481	0.226	1.022
−2 Log likelihood: 205.720						
Chi-squared: 6.594						
$P = 0.037$						

vaccination was not administered in a randomized, controlled mode. However, there was no statistical difference between baseline characteristics of vaccinated and unvaccinated patients (see Table I). (2) The absence of effect on definite pneumococcal pneumonia could be a consequence of the low sensitivity of diagnostic techniques for the diagnosis of *S. pneumoniae* as an etiologic factor of pneumonia; however, the protective effect of vaccine was not evident in respect of pneumonia of pneumococcal and unknown causes (data not shown) nor in respect of all bacterial pneumonias were considered.

To our knowledge, this is the first investigation that has estimated pneumococcal vaccine effectiveness among HIV-infected patients differentiating those who had benefited from HAART. We observed a lower incidence (but not reaching statistical significance) of all bacterial pneumonias only in a subgroup of our patients, those with a CD4+ T cell count lower than 200/μl and immunological response to HAART. Thus, in the HAART era, recommendation of polysaccharide pneumococcal vaccination could be limited to this group of patients. And consequently, other methods to protect against *S. pneumoniae* must be considered. One of these could be the improvement of vaccine-induced protection, such as alternative vaccination strategies utilizing pneumococcal capsular polysaccharide protein-conjugate vaccines. However, these conjugate vaccines contain fewer capsular serotypes, and antibody responses to primary immunization are no greater than those to the current 23-valent polysaccharide vaccine in patients with HIV disease [Ahmed et al., 1996]. Therefore, it may more cost-effective to concentrate effort on strategies to improve adherence to HAART, as this has been shown to be associated unequivocally with a reduction in the incidence of pneumonia.

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