Incidence, Timing, and Determinants of Bacterial Pneumonia Among HIV-Infected Patients: Data From the ICONA Foundation Cohort

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Background: The aim of the study was to evaluate incidence and determinants of bacterial pneumonia (BP) after starting combination antiretroviral therapy (cART) in the Italian Cohort of Antiretroviral-Naive Patients.

Methods: Patients free from BP at cART initiation enrolled between 1996 and 2011 were analyzed. Kaplan–Meier curves were calculated to estimate the time to the first episode of BP; uni- and multivariable Cox proportional hazard models, with time-updated covariates, were applied to identify the risk factors of the first episode of BP.

Results: Four thousand nine hundred forty-two patients were followed for a median of 63.7 months (interquartile range: 23.6, 106.7); 73% were men, median age 36 years (interquartile range: 32, 42), 35% hepatitis C virus antibody positive, 28% smokers, 15% with an AIDS diagnosis (not BP) before cART, 46% with nadir $CD4^+$ T-cell count $\leq$200 cells per microliter. During 27,569 person years, 137 patients developed 156 BPs, for a crude incidence of 5.66 [95% confidence interval (CI): 4.81 to 6.62] per 1000 person years. The probabilities of first BP at 3, 5, 10, and 14 years from cART initiation were 2.0% $\pm$ 0.22%, 2.9% $\pm$ 0.28%, 4.3% $\pm$ 0.42%, and 5.7% $\pm$ 0.75%, respectively. The occurrence of a first BP was associated with low nadir $CD4^+$ [hazard ratios (HR) (per 100 cells/μL higher) = 0.86, 95% CI: 0.79 to 0.94], low current $CD4^+$ [HR (per 100 cells/μL higher) = 0.88, 95% CI: 0.84 to 0.92], high $CD8^+$ [HR (per 100 cells/μL higher) = 1.02, 95% CI: 1.01 to 1.03], low hemoglobin [HR (per g/dL higher) = 0.74, 95% CI: 0.71 to 0.78], and unfavorable virological outcome [HR (HIV-RNA >50 vs <50 copies/mL) = 1.29, 95% CI: 1.04 to 1.60] in addition to older age, male gender, non-Italian nationality, smoking, and longer time to cART initiation.

Conclusions: BP is an infrequent clinical event in the cART era and is associated with traditional risk factors, viroimmunological failure to cART, and low hemoglobin.

Key Words: bacterial pneumonia, incidence, risk factors, antiretroviral-naive patients

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INTRODUCTION

In the era of the combination antiretroviral therapy (cART), bacterial pneumonia (BP) is still a major cause of morbidity and mortality of HIV-infected patients.[1,2] Recurrent BP was considered a marker of impaired immune function and therefore was included in the 1993 Centers for Disease Control and Prevention classification as an AIDS-defining illness.[3] In industrialized countries, approximately 10% of the causes of severe morbidity and 5% of the causes of death of HIV+ patients are related to BP,[1,2] and even a single BP episode is associated with increased morbidity and mortality.[4–6] In the last years, even if a marked reduction in AIDS-associated opportunistic infections is well documented,[7] the incidence of BP did not decrease in parallel with that of other infections and high rates of BP have been reported.[8,9]

Reduction in the long-term survival after BP may be influenced by different factors, including increased viral replication and viral burden, increased inflammation, and changes in immune status.[10] The degree of immunosuppression has been associated with increased risk of pneumonia. However, although the risk to develop BP is higher among HIV+ patients with low CD4 cell counts, rates of BP remain elevated even among persons with a level of CD4 >500 cells per microliter.[11] Furthermore, in a recent follow-up of the Strategies for Management of Antiretroviral Therapy study group, the increased risk of opportunistic diseases correlated with the viral load and was independent of the $CD4^+$ cell

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count.[12] Multiple risk factors contribute to increase the risk of pneumonia, including age, intravenous drug use, smoking of illicit drugs, and alcoholism.[9,13–15] Tobacco smoking, which is highly prevalent in HIV-infected populations, is also independently associated with an increased risk of BP.[13]

To investigate the incidence, timing, and determinants of BP, in HIV+ patients of ICONA (Italian Cohort of Antiretroviral-Naive Patients), we have evaluated the rate and risk factors for developing at least one episode of BP after starting cART.

METHODS

Study Population

The study population included patients who, at the beginning of cART, had never experienced BP and have been enrolled in the multicenter ICONA Foundation Study, during the period August 1996 to June 2011. Data of the ICONA are prospectively collected and centrally stored into a database: each center is asked 4 times per year (ie, every 3 months) to send the data prospectively collected on each patient included in the cohort. Data collected include information on comorbidities, thus including pulmonary diseases. In addition, data monitoring is performed once a year to ensure accurate and complete data collection.

Demographic and clinical characteristics and the data regarding immunological, virological, and hematological parameters (hemoglobin, white blood cells, neutrophils, and platelets) were extracted from the ICONA database. Information on cART included type of first-line therapy [mono/dual (ART initiation with 1 or 2 antiretroviral drugs) versus highly active antiretroviral therapy (HAART) (ART initiation with ≥3 antiretroviral drugs)] and years of cumulative exposure to cART. Data on pneumococcal vaccination were not collected.

Definition of BP

The diagnosis of BP was ascertained at each center of ICONA by history and medical and radiological record reviews; the diagnosis was based on the presence of a progressive infiltrate on a chest radiograph, clinical response to antibacterial medications, and, when available, on a sputum culture positive for any microorganism. The following diagnoses of pneumonia were excluded: *Pneumocystis jiroveci* pneumonia, tuberculosis or other mycobacteria, and viral pneumonia. Case definitions were based on the evaluation of the treating physicians.

Statistical Analysis

Results were described as median and interquartile range (IQR), or number of cases (percent), as appropriate. The crude incidence rates of BP, with the corresponding 95% confidence intervals (CIs), were calculated per 1000 person years of follow-up (PYFU) as the total number of BP episodes divided by the time contributed by all subjects (in this calculation, time was censored at the last patient's cohort visit).

Follow-up was counted from the date of the cART start (baseline) to the date of first BP, for patients who had at least one event, or the date of last patient's cohort visit if BP did not occur. Patients with a first BP before ART start were excluded from the analyses.

Virological suppression was defined by the achievement of at least one value of HIV-RNA <50 copies per milliliter after the start of cART; time to virological suppression was defined as the interval time between the start of cART and the achievement of the first HIV-RNA <50 copies per milliliter. Two consecutive values of HIV-RNA >50 copies per milliliter after the achievement of virological suppression were used to define virological failure; time to virological failure was defined as the interval time between the achievement of the first HIV-RNA <50 copies per milliliter and the first of 2 consecutive values of HIV-RNA >50 copies per milliliter.

Associations between clinical variables and the occurrence of first BP were examined using χ^2 or Fisher exact tests. The Wilcoxon rank sum test was applied to detect differences among subjects with or without BP with respect to distributions of continuous variables. The Wilcoxon sign rank test was used to detect significant changes from the start of cART for the laboratory parameters.

Time to the first episode of BP (since cART initiation) was estimated by Kaplan–Meier curves and compared by the log rank test. The relation between demographic, clinical, and laboratory parameters and the occurrence of the first BP was analyzed by uni- and multivariable Cox proportional hazard models. The following characteristics were considered: age, gender (male vs female), education (elementary vs intermediate vs unknown), mode of HIV transmission (intravenous drug users, IDU, vs other), hepatitis C virus (HCV) antibody (positive vs negative vs unknown), a diagnosis of AIDS before cART (yes vs no), nadir $CD4^+$ (per 100 cells/mm^3 higher), smoking (yes vs no vs unknown), nationality (Italian vs non-Italian), months since enrollment to cART start, $CD4^+$, $CD8^+$, HIV-RNA (≤50 vs >50 copies/mL), hemoglobin, white blood cells, platelets, and neutrophils; smoking status, $CD4^+$, $CD8^+$, HIV-RNA, hemoglobin, white blood cells, platelets, and neutrophils were examined as time-dependent variables. Factors notably known to be or those that were found ($P < 0.05$) associated with the occurrence of BP were entered into the multivariable model. Hazard ratios (HR) and the corresponding 95% CIs were reported.

All tests were 2 sided, and a P value < 0.05 was considered statistically significant. Analyses were performed using the SAS software (release 9.2; SAS Institute, Cary, NC).

RESULTS

A total of 4942 patients started cART without having had a BP and were included in the analyses. During 27,569 person years of observation [median follow-up: 5.03 (IQR: 1.84, 8.62) years], 156 BPs occurred in 137 patients. Multiple episodes were infrequent: 124 (90%) patients had 1 episode, 11 (8%) had 2 episodes, 1 (<1%) had 3 episodes, and 1 (<1%) had 7 episodes. The crude rate of BP was 5.66 (95% CI: 4.81 to 6.62) episodes per 1000 person years.

Etiology of BP was unknown in 80 cases, whereas among the other 57 patients, the most frequent pathogens were *Streptococcus pneumoniae* (23), followed by *Staphylococcus aureus* (9), *Haemophilus* spp (7), *Klebsiella pneumonia* (4), *Legionella* (4), *Pseudomonas aeruginosa* (5), *Escherichia coli* (2), *Mycoplasma pneumonia* (1), *Chlamydia* (1), and *Acynetobacter baumannii* (1).

Table 1 shows the baseline characteristics of the patients classified as those who developed at least 1 BP (N = 137) and those who did not (N = 4805).

Subjects who experienced BP were more frequently IDU and coinfected with HCV, had a lower education degree, lower percentages of $CD4^+$ T cells, and lower values of nadir $CD4^+$; hemoglobin values were comparable with those subjects without BP. Eight hundred twenty-eight (17%) patients started a mono/dual ART (and, subsequently, HAART), whereas 4114 started HAART (83%) as first-line therapy. Three hundred eighteen (6%), 1563 (32%), and 3061 (62%) patients started a nucleoside reverse transcriptase inhibitor–based, nonnucleoside reverse transcriptase inhibitor–based, or protease inhibitor–based cART, respectively. There were 828 subjects who started a mono/dual ART and switched to HAART after 16.4 (IQR: 5.9, 39.6) months. In these patients, the first episode of BP occurred after a median of 1.47 (IQR: −0.32, 3.12) years after the beginning of HAART.

Death occurred in 21 (15%) and 272 (6%) subjects with or without BP, respectively ($P < 0.0001$). Eleven causes of death were HIV related, 3 related to other diseases, 2 cardiovascular events, 1 liver-related death, and 4 unknown. Among patients with BP, death occurred after a median of 12.6 (IQR: 0.3, 34.4) months since the first episode of BP.

Concerning CD4 counts, among subjects with at least one event at the time of the first BP occurrence, 46 (34%) had ≤200 cells per microliter, 31 (23%) had 201–350 cells per microliter, and 60 (44%) had >350 cells per microliter, whereas median HIV-RNA was 2.79 (1.70–4.65) ($\log_{10}$ copies/mL).

Among patients who developed BP, the median follow-up before the first episode of BP was 22.7 (IQR: 7.2, 56.8) months; during this period, significant immunological changes were observed [$CD4^+$: 48 (−51, +199) cells/μL, $P = 0.002$; $CD8^+$: 36 (−378, +304) cells/μL, $P = 0.894$].

Upon cART initiation, 758 patients (16%) never achieved virological suppression: 43 (34%) among those who developed BP and 715 (15%) among those who did not, respectively ($P < 0.0001$). Out of the 4184 (84%) patients who reached virological success during follow-up [median time to virological suppression: 6.3 (IQR: 3.4, 15.7) months], no significant differences were observed among subjects with or without BP ($P = 0.285$). At the time of the first BP, 48 (35%) patients had an undetectable viral load and 89 (65%) had a positive viremia.

First BP episode occurred 2.8 (IQR: 1.0, 5.4) years after the achievement of virological suppression, when reached. Moreover, the time to the first BP was shorter among patients who maintained virological suppression (n = 49), when compared with those who did not (n = 45) [1.8 (IQR: 0.9, 3.5) years and 6.0 (IQR: 3.8, 9.3) years, respectively, $P < 0.0001$].

Overall, the probabilities (± standard error) of the first BP at 3, 5, 10, and 14 years since cART initiation were 2.0% ± 0.22%, 2.9% ± 0.28%, 4.3% ± 0.42%, and 5.7% ± 0.75%, respectively. The probability of having BP was similar among strata (quartiles) of calendar year of cART initiation (1996–1998, 1999–2000, 2001–2006, and 2007–2011; log rank test: $P = 0.111$; data not shown).

As shown in Figure 1, the probability of first BP was higher in patients with lower values of nadir $CD4^+$ (nadir $CD4^+$ ≤200 vs >200 cells/mm^3, $P = 0.050$), in the presence of a HCV coinfection (positive vs negative, $P = 0.006$), and among smokers (smoker vs nonsmoker, $P < 0.0001$). Univariable and multivariable HR were evaluated to find out factors associated with BP (Table 2). At multivariable analysis, as expected, traditional risk factors for BP were predictive of the event: the risk of first BP increased with age and was more likely among men as compared with women, among smokers as compared with nonsmokers, among non-Italian as compared with Italian subjects. In addition, BP was more likely to occur in subjects with positive HIV viremia, low values of nadir $CD4^+$, low values of hemoglobin, low values of $CD4^+$, high values of $CD8^+$, and delayed cART initiation.

DISCUSSION

The present study has shown that BP is a relatively uncommon event among HIV-infected patients. Data on BP incidence are not consistent among different studies, varying from 8.5 to 28.0 PYFU.[7,11,15] In our cohort, the rate of incidence was much lower, that is, 5.66 per 1000 PYFU. Because patients enrolled in ICONA are Italians, we cannot exclude a role for a milder climate.

Concerning the etiology, it was impossible to establish a causative agent in all patients. However, *S. pneumoniae* remains the most frequent pathogen, as previously described.[15] This is particularly relevant because either primary infection or recurrent episodes of *S. pneumoniae* can be successfully prevented by vaccination even in patients with HIV infection, especially when the vaccine is administered to patients with high $CD4^+$ T-cell count.[16–18] Concerning risk factors for the development of BP, we found significant associations with demographic characteristics, HIV infection–related factors (with immune suppression and viremia playing a major role), and lifestyle–related factors (with smoking playing a well-known main role).

The importance of age on BP has already been reported by Goulet et al[19]: older HIV-infected veterans, aged ≥50 years, had higher odd of pulmonary disease than younger HIV-infected veterans or older HIV-uninfected veterans.

We found that men were more likely to develop BP than women, according to previous data showing that such incidence is higher in men than in women, in all age groups considered.[20,21] These differences may be a consequence of genetic differences linked to X-chromosome, in the expression of steroid hormones, and finally in anatomy.[22] Italian subjects were less likely to experience BP: this might be related to a high socioeconomic status, with an easier access to the National Health Care System. It is to note that most immigrants came from African countries and are not used to Italian winter temperatures, which are milder than in Northern Europe, but much colder than in their countries of origin.

TABLE 1. Demographic and Clinical Characteristics of the Study Patients at cART Initiation

Characteristic	Overall (N = 4942)	With BP (N = 137)	Without BP (N = 4805)	*P*
Age (yrs)	37 (32–43)	37 (33–42)	37 (32–43)	0.821*
Gender				0.846†
Males	3586 (72.6%)	101 (73.7%)	3485 (72.5%)	
Females	1536 (27.4%)	36 (26.3%)	1320 (27.5%)	
Nationality				0.989†
Italian	4499 (91.0%)	127 (92.7%)	4372 (91.0%)	
Non-Italian	443 (9.0%)	10 (7.3%)	433 (9.0%)	
Education				0.015†
Elementary degree	2075 (42.0%)	72 (52.5%)	2003 (41.7%)	
Intermediate degree	1520 (30.8%)	26 (19.0%)	1494 (31.1%)	
Unknown	1347 (27.2%)	39 (28.5%)	1308 (27.2%)	
Smoking				<0.0001†
Yes	2252 (45.6%)	66 (48.2%)	2186 (45.5%)	
No	2160 (43.7%)	25 (18.2%)	2135 (44.4%)	
Unknown	530 (10.7%)	46 (33.6%)	484 (10.1%)	
Alcohol consumption				0.999†
Yes	742 (15.0%)	20 (14.6%)	722 (15.0%)	
No	4200 (85.0%)	117 (85.4%)	4083 (85.0%)	
Mode of HIV transmission				<0.0001†
IDU	1389 (27.9%)	63 (46.0%)	1326 (27.6%)	
MSM	1261 (25.5%)	16 (11.7%)	1245 (25.9%)	
Heterosexual	1960 (39.7%)	47 (34.3%)	1913 (39.8%)	
Other	69 (1.4%)	1 (0.7%)	68 (1.4%)	
Unknown	263 (5.3%)	10 (7.3%)	253 (5.3%)	
HCV antibody				0.002†
Positive	1741 (35.2%)	67 (48.9%)	1674 (34.8%)	
Negative	2819 (57.0%)	59 (43.1%)	2760 (57.4%)	
Unknown	382 (7.7%)	11 (8.0%)	371 (7.7%)	
HBsAg				0.067†
Positive	357 (7.2%)	9 (6.6%)	348 (7.2%)	
Negative	4196 (84.9%)	110 (80.3%)	4086 (85.0%)	
Unknown	389 (7.9%)	18 (13.1%)	371 (7.7%)	
Diagnosis of AIDS before cART‡				0.089†
Yes	747 (15.1%)	28 (20.4%)	719 (15.0%)	
No	4195 (84.9%)	109 (79.6%)	4086 (85.0%)	
Nadir $CD4^+$	220 (97–317)	173 (38–307)	221 (99–317)	0.014*
≤200 (cells/mm^3)	2223 (45.0%)	71 (51.8%)	2152 (44.8%)	0.049†
>200 (cells/mm^3)	2719 (55.0%)	66 (48.2%)	2653 (55.2%)	
$CD4^+$ (cells/mm^3)	280 (143–411)	241 (88–395)	281 (144–413)	0.156*
CD4 (%)	17.9 (11.0–25.0)	15.6 (8.0–22.6)	18.0 (11.0–25.0)	0.019*
$CD8^+$ (cells/mm^3)	832 (550–1197)	805 (540–1268)	832 (550–1192)	0.971*
CD8 (%)	56.4 (48.0–65.4)	56.1 (48.0–67.0)	56.5 (48.0–65.2)	0.804*
HIV-RNA (log_{10} copies/mL)	4.79 (4.24–5.28)	4.94 (4.20–5.28)	4.78 (4.24–5.28)	0.850*
Hemoglobin (g/dL)	13.5 (12.2–14.7)	13.0 (11.8–14.3)	13.5 (12.2–14.7)	0.032*
White blood cells (10^6 cells/mm^3)	4860 (3800–6015)	4710 (3800–6460)	4865 (3800–6000)	0.643*
Neutrophils (10^6 cells/mm^3)	2500 (1882–3350)	2468 (1810–3430)	2500 (1887–3350)	0.967*
Platelet (10^9 cells/L)	184 (142–229)	181 (143–230)	184 (142–229)	0.840*
AST (U/L)	29 (21–45)	34 (22–56)	28 (21–45)	0.027*
ALT (U/L)	30 (20–51)	32 (18–60)	30 (20–51)	0.590*
Months since enrollment to cART start (mo)	1.2 (0–12.9)	1.3 (0–11.7)	1.2 (0–12.9)	0.773*

*Wilcoxon rank sum test to detect significant differences between patients with or without BP in relation to continuous variables.
†χ^2 Test to detect significant differences between patients with or without BP in relation to categorical variables.
‡The diagnosis did not include BP.
IDU, intravenous drug users; MSM, men who have sex with men; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBsAg, hepatitis B surface Antigen.

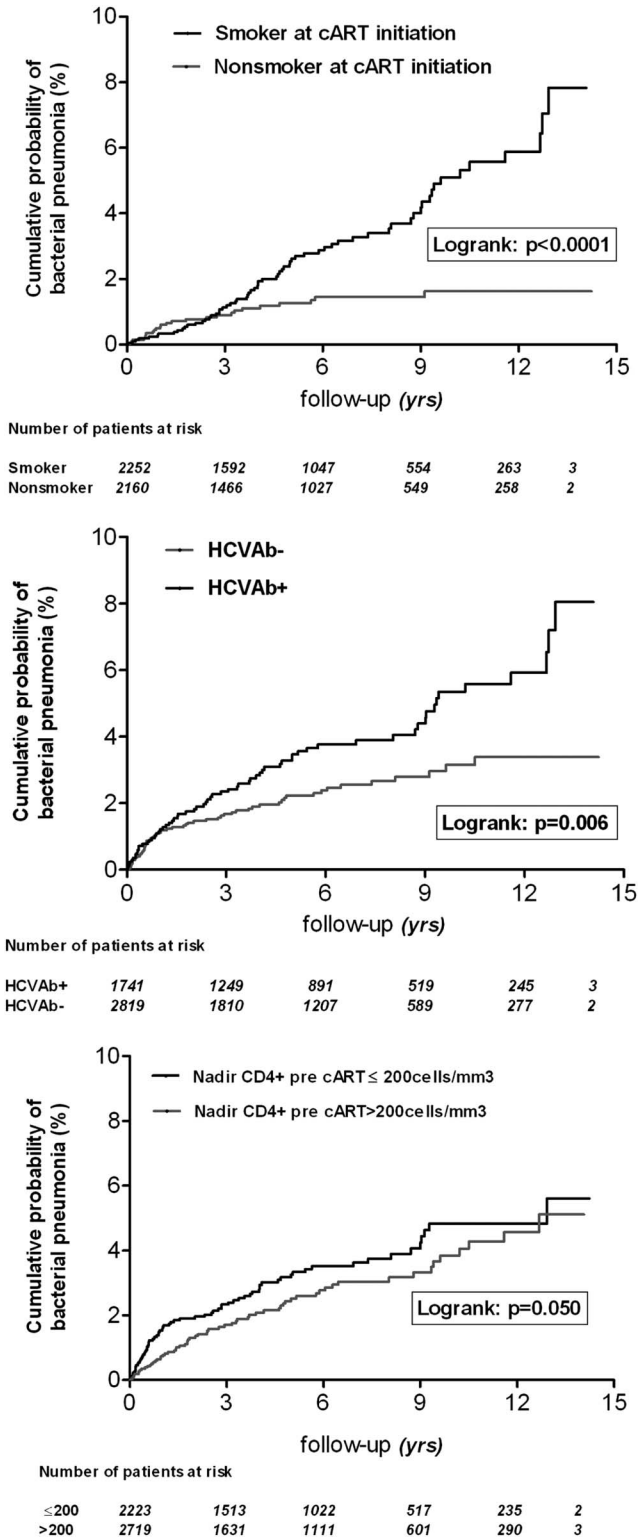

FIGURE 1. Time to first BP according to smoking status at cART initiation (smoker vs nonsmoker), HCV antibody (positive vs negative), nadir CD4+ (≤200 vs >200 cells/μL).

Concerning CD4, either nadir or current CD4+ T-cell count was associated with the development of BP; it is to note that patients with a CD4+ T-cell count >350 cells per microliter developed BP. The fact that immune suppression could favor the onset of BP was already known because recurrent episodes are considered an AIDS-defining event.

In our study, most patients who developed BP had a detectable viral load, likely because of treatment failure or treatment discontinuation. Viral load has a role, which is independent from immune deficiency. This is confirmed by data from Collaboration of Observational HIV Epidemiological Research in Europe showing that patients with a CD4+ T-cell count lower than 200 cells per microliter could be protected from a first or a recurrent episode of *P. jiroveci* pneumonia, in the absence of prophylaxis, if they have an undetectable HIV plasma viremia.[23] These data go in the same direction of those from the Strategies for Management of Antiretroviral Therapy trial: indeed, the inflammation related to HIV replication could favor the onset of AIDS and non-AIDS diseases.[12] The earlier BP occurrence among patients who achieved and maintained virological suppression as compared with those who did not was mainly related to a delayed cART initiation and slightly higher HIV-RNA values at cART initiation observed in these patients (data not shown).

Concerning blood markers, anemia has been related to the onset of BP, and indeed, our results confirmed the association of anemia with a poorer outcome. Most studies evidenced a possible role of anemia on survival,[24,25] and anemia was recently included in a combined prognostic index for survival, the Veterans Ageing Cohort Study (VACS) index,[26,27] and in several patients can improve during ART.[28] If anemia persists or develops after treatment, different phenomena can be suspected, including a poor adherence, emerging HIV resistance, or additional causes of chronic inflammation.[27] It is also possible that this marker may be a proxy of a general impairment of the bone marrow that could lead to a worse prognosis not only in HIV infection but also in other chronic diseases, such as cancer.[29]

Recurrent episodes of BP are a risk factor for the development of lung cancer,[30] and at the beginning of cART era, there were some data showing an increase in the incidence of recurrent BP. However, our data show that BP is, at present, a relatively rare event.[31] Tobacco smoking is a very dangerous habit, being a major risk factor for cardiovascular events, osteoporosis, and also for pulmonary pathologies increasing risk of pneumococcal bacteremia and invasive pneumococcal disease.[32,33] Because approximately 40%–70% of people living with HIV smoke, in contrast with 21% who smoke among all US adults,[34,35] clinicians should use all available strategies to convince patients to smoking cessation (being well aware that this is not easy at all).

We found that the risk of BP increased with a longer time spent without antiretroviral treatment because a delayed cART initiation slightly increased the chance of developing BP. The beneficial effects of early ART initiation have already been reported in previous studies,[36–39] showing that the excess of AIDS or death associated with deferred initiation of combination therapy became more pronounced, that is, when the CD4+ T-cell count threshold for starting treatment decreased.

TABLE 2. Univariable and Multivariable Proportional Hazard Models: Risk of BP (First Episode) According to Demographic and Clinical Characteristics

	Univariable Analysis			Multivariable Analysis		
Characteristic	**HR**	**95% CI (HR)**	***P***	**HR**	**95% CI (HR)**	***P***
Age (per 10 yrs older)	1.025	0.984 to 1.067	0.228	1.312	1.177 to 1.461	<0.0001
Gender						
Males vs females	1.328	1.215 to 1.451	<0.0001	1.596	1.255 to 2.029	0.0001
Nationality						
Non-Italian vs Italian	1.250	1.088 to 1.436	0.002	1.567	1.073 to 2.290	0.020
Education			<0.0001			0.0001
Intermediate degree vs elementary degree	0.461	0.419 to 0.508	<0.0001	1.140	0.901 to 1.444	0.275
Unknown vs elementary degree	0.825	0.750 to 0.909	<0.0001	0.517	0.368 to 0.727	0.0001
Current smoking			<0.0001			<0.0001
Yes vs no	1.714	1.578 to 1.861	<0.0001	2.623	2.060 to 3.339	<0.0001
Unknown vs no	4.532	3.960 to 5.186	<0.0001	10.38	6.671 to 15.92	<0.0001
Mode of HIV transmission						
IDU vs other	1.517	1.407 to 1.635	<0.0001	1.039	0.746 to 1.448	0.819
HCV antibody			<0.0001			0.003
Positive vs negative	1.314	1.216 to 1.421	<0.0001	0.849	0.625 to 1.154	0.296
Unknown vs negative	2.247	1.971 to 2.562	<0.0001	1.960	1.233 to 3.116	0.004
Diagnosis of AIDS before cART*						
Yes vs no	1.903	1.736 to 2.086	<0.0001	1.337	0.989 to 1.809	0.059
Nadir CD4 before cART (per 100 cells/mm^3 higher)	0.935	0.912 to 0.959	<0.0001	0.860	0.792 to 0.935	0.0004
Current HIV-RNA						
>50 vs ≤50 (copies/mL)	2.119	1.933 to 2.323	<0.0001	1.292	1.043 to 1.600	0.019
Current CD4 (per 100 cells/mm^3 higher)	0.915	0.894 to 0.935	<0.0001	0.884	0.844 to 0.924	<0.0001
Current CD8$^+$ (per 100 cells/mm^3 higher)	1.028	1.018 to 1.037	<0.0001	1.021	1.008 to 1.032	0.0007
Current hemoglobin (per g/dL higher)	0.733	0.712 to 0.754	<0.0001	0.743	0.708 to 0.780	<0.0001
Current white blood cells (per 1000–10^6 cells/mm^3 higher)	0.996	0.968 to 1.000	0.769	0.999	0.981 to 1.000	0.635
Current neutrophils (per 1000–10^6 cells/mm^3 higher)	1.005	0.986 to 1.016	0.508	0.999	0.974 to 1.012	0.885
Current platelet (per 100–10^9 cells/L higher)	0.940	0.864 to 1.000	0.144	0.992	0.938 to 1.001	0.412
Months since enrollment to cART start (per 6 mo longer)	0.987	0.985 to 0.989	<0.0001	1.035	1.007 to 1.062	0.012

*The diagnosis did not include BP.
95% CI (HR), 95% CI of HR; IDU, intravenous drug users.

Our study has some possible limitations, including: (1) the fact that ICONA is a cohort that includes Departments of Infectious Diseases in main universities or hospitals. Because some episodes of BP could have been treated by general practitioners, we cannot exclude that underreporting the incidence of BP may have occurred; (2) ICONA collects main demographic, clinical, and laboratory data but does not have a specific form for BP or other pulmonary diseases. Thus, for the analysis shown here, we could use only the data recorded in the cohort database; (3) we could not collect data on pneumococcal vaccination, and thus, we could not evaluate a possible protective role and its influence on the low incidence of BP; (4) we had no data on chronic obstructive pulmonary disease, and thus, we could not evaluate a possible role of this disease as a risk factor for BP in our population; and (5) finally, our study does not have the statistical power to evaluate the risk factors for recurrences. However, it is possible that cART, as in the case of other opportunistic infections, may have a role in preventing them.[23]

In conclusion, even considering the possible problem of underreporting, it seems that BP is uncommon among HIV+ patients living in Italy and enrolled in ICONA. Classical risk factors as immune deficiency and smoking are associated with BP onset, but a major role seems to be played by uncontrolled HIV viremia and anemia. Thus, to prevent BP, clinicians should prescribe pneumococcal vaccine and cART and suggest strategies for smoking cessation to their patients.

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