Bacterial Pneumonia, HIV Therapy, and Disease Progression among HIV-Infected Women in the HIV Epidemiologic Research (HER) Study

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Background. To determine the rate and predictors of community-acquired bacterial pneumonia and its effect on human immunodeficiency virus (HIV) disease progression in HIV-infected women, we performed a multiple-site, prospective study of HIV-infected women in 4 cities in the United States.

Methods. During the period of 1993–2000, we observed 885 HIV-infected and 425 HIV-uninfected women with a history of injection drug use or high-risk sexual behavior. Participants underwent semiannual interviews, and $CD4^+$ lymphocyte count and viral load were assessed in HIV-infected subjects. Data regarding episodes of bacterial pneumonia were ascertained from medical record reviews.

Results. The rate of bacterial pneumonia among 885 HIV-infected women was 8.5 cases per 100 person-years, compared with 0.7 cases per 100 person-years in 425 HIV-uninfected women ($P < .001$). In analyses limited to follow-up after 1 January 1996, highly active antiretroviral therapy (HAART) and trimethoprim-sulfamethoxazole (TMP-SMX) use were associated with a decreased risk of bacterial pneumonia. Among women who had used TMP-SMX for 12 months, each month of HAART decreased bacterial pneumonia risk by 8% (adjusted hazard ratio [HR_{adj}], 0.92; 95% confidence interval [CI], 0.89–0.95). Increments of 50 $CD4^+$ cells/mm^3 decreased the risk (HR_{adj}, 0.88; 95% CI, 0.84–0.93), and smoking doubled the risk (HR_{adj}, 2.12; 95% CI, 1.26–3.55). Bacterial pneumonia increased mortality risk (HR_{adj}, 5.02; 95% CI, 2.12–11.87), with adjustment for $CD4^+$ lymphocyte count and duration of HAART and TMP-SMX use.

Conclusions. High rates of bacterial pneumonia persist among HIV-infected women. Although HAART and TMP-SMX treatment decreased the risk, bacterial pneumonia was associated with an accelerated progression to death. Interventions that improve HAART utilization and promote smoking cessation among HIV-infected women are warranted.

Bacterial pneumonia is a major source of morbidity and mortality among HIV-infected individuals, and it occurs up to 25 times more frequently among HIV-infected persons than among the general population [1–3]. The Centers for Disease Control and Prevention reported that pneumonia due to an unspecified organism, excluding *Pneumocystis carinii* pneumonia (PCP), was the leading cause of death among HIV-infected persons in the United States during 1990–1999 [4]. With the advent of HAART, marked reductions in AIDS-associated opportunistic infections and mortality have been well described [5–7]. Nonetheless, in the HAART era, the incidence of bacterial pneumonia may not be decreasing in parallel with the incidence of other opportunistic infections.

Recent studies have observed high rates of bacterial pneumonia of 7.7 and 9.1 cases per 100 person-years [8, 9]. In a cohort of male injection drug users in

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Puerto Rico, the proportion of persons with bacterial pneumonia increased from 28.7% in 1992 to 35.7% in 2000 [10]. In Europe, the proportion of cases of AIDS associated with recurrent bacterial pneumonia increased 3-fold (from 1.5% to 4.6%) after the introduction of HAART [11]. Bacterial pneumonia was the most frequent hospital discharge diagnosis in a longitudinal study of HIV-infected persons in the Bronx during the period of 1996–2000 [12].

The use of trimethoprim-sulfamethoxazole (TMP-SMX) to prevent PCP, in addition to HAART, may have the salutary effect of reducing the incidence of bacterial pneumonia among persons with advanced HIV infection [13, 14]. However, results have not been uniform in this direction, and the effect of HAART plus TMP-SMX therapy has not been well examined in established prospective studies [9, 15, 16].

Studies of bacterial pneumonia and HIV infection have largely focused on male injection drug users and men who have sex with men [17, 18]. However, HIV-infected women may be at higher risk for bacterial pneumonia than HIV-infected men [13, 14, 19–21]. Lower rates of HAART use among women have been reported [22, 23]. A review of AIDS surveillance in Europe reported that women were more likely than men to have recurrent bacterial pneumonia as an AIDS-defining illness [24]. Floris-Moore et al. [12] observed that, in the HAART era, women had a higher risk of all-cause hospitalization and a higher rate of bacterial pneumonia hospitalization than did men. To further elucidate the rate of and risk factors for bacterial pneumonia, including duration of HAART and TMP-SMX use, we studied HIV-infected women who participated in the HER (HIV Epidemiologic Research) Study, a multiple-site, prospective study of the natural history of HIV disease in women [25].

METHODS

As described elsewhere [25–27], from April 1993 to January 1995, 885 HIV-infected and 425 at-risk women were recruited in the HER Study from 4 academic sites in New York; Baltimore, Maryland; Detroit, Michigan; and Providence, Rhode Island. Women aged 16–55 years were enrolled if they provided signed, written informed consent and reported injection drug use since 1985 or reported ⩾1 high-risk sexual behavior as follows: ⩾5 sex partners in the previous 5 years, sex with a man who was known or suspected to be HIV infected, or exchange of sex for money or illicit drugs. Women with a clinical AIDS diagnosis were excluded from the study; women with a $CD4^+$ lymphocyte count <200 cells/mm^3 were enrolled. The study was not designed to provide medical care or diagnostic evaluation; women were referred to appropriate sources of care. The institutional review boards of all participating institutions approved the study.

Participants were observed semiannually and underwent standardized interviews to assess sociodemographic characteristics, medical history, intercurrent hospitalizations, use of HAART [28], TMP-SMX use, and use of cigarettes, alcohol, and illicit drugs. Blood samples were drawn to detect serum HIV antibody (by EIA with Western blot confirmation) among participants with unknown HIV serostatus. Among HIV-seropositive participants, $CD4^+$ lymphocyte count and (starting in 1997) HIV load (HIV viral load test; Chiron) were measured.

Pneumonia-related events were ascertained by history and medical record review. Report of hospitalization led to review of hospital records by trained medical record abstractors and completion of a pneumonia abstraction form, when applicable. This form assessed clinical data on the basis of predetermined criteria for bacterial pneumonia. A national death index search assessed mortality. Identification of deaths prompted a request for death certificates and review of medical records from the period just before the subject's death.

Definition of bacterial pneumonia. Diagnosis of "definitive" bacterial pneumonia required the presence of a new or progressive infiltrate on a chest radiograph and either a sputum culture positive for *Streptococcus pneumoniae, Haemophilus influenza, Klebsiella* species, *Staphylococcus aureus, Pseudomonas* species, *Enterobacter* species, or *Legionella* species or a positive blood or pleural fluid culture result (and no other identified source). Diagnosis also required either a clinical response to antibacterial medication or a positive sputum Gram stain result and either cough, shortness of breath, or a respiratory rate >20 breaths/min

Diagnosis of "probable" bacterial pneumonia required a new or progressive infiltrate on a chest radiograph, no diagnosis of PCP, and either a clinical response to antibacterial medication or a positive sputum Gram stain result and an oral temperature >37.8°C. Diagnosis also required either cough, shortness of breath, or a respiratory rate >20 breaths/min. Diagnosis of "presumed" bacterial pneumonia required a physician discharge diagnosis of such, admission chest radiograph with an infiltrate, and for the case to have not met the criteria for PCP.

For all classes of pneumonia, the diagnostic radiograph was dated within 48 h after admission. Patients were excluded if the chest radiograph revealed bilateral interstitial infiltrates and/or there were test results positive for PCP, mycobacteria, or malignancy in the upper or lower respiratory tracts. One case in which endocarditis was definitively diagnosed was also excluded. A sputum Gram stain result was positive if ⩾2+ granulocytes and organisms were reported, negative if granulocytes but no organisms were present, and inadequate if <2+ granulocytes were seen, regardless of whether organisms were present.

Statistical analysis. The HER Study enrollment began in April 1993, and follow-up ended on 1 April 2000. Data from interviews and medical record abstractions of bacterial pneumonia hospitalizations during this period were included in the

analyses. All cases of bacterial pneumonia that met the definitions (68 definitive cases, 14 probable cases, and 247 presumed cases) were included, because univariate analyses that excluded the presumed cases yielded similar results. For 14 women who experienced seroconversion during the study, the follow-up time from first positive HIV antibody test result was included.

Associations between risk behaviors, clinical variables, and bacterial pneumonia were examined using χ^2 or Fisher's exact tests. Rates of pneumonia were calculated as the number of episodes divided by time contributed by participants.

Among HIV-infected participants, time to the first episode of bacterial pneumonia was estimated by Kaplan-Meier curves. Cox proportional hazards models were used to examine the effect of age, race, education, cigarette smoking, injection drug use, alcohol use, public assistance, $CD4^+$ lymphocyte count, HIV load, HAART use, and TMP-SMX use on time to first episode of pneumonia and time to death among HIV-infected participants. $CD4^+$ lymphocyte count, HIV load, and alcohol and injection drug use were examined as time-dependent variables. HAART and TMP-SMX were assessed as duration of use in months. A separate analysis was performed including only follow-up time after the $CD4^+$ lymphocyte count decreased to $\leq$200 cells/mm^3. In analyses of time to first episode of bacterial pneumonia and death, follow-up was restricted to visits after 1 January 1996, when HAART was uniformly available. Analyses were performed using SPSS software, version 10.0 (SPSS), and SAS software, version 8.1 (SAS Institute).

RESULTS

Among 885 HIV-infected women, baseline $CD4^+$ lymphocyte counts were >500 cells/mm^3 in 289 (32.6%), 201–500 cells/mm^3 in 436 (49.3%), and $\leq$200 cells/mm^3 in 155 (17.5%). Median viral load at study entry was 10,383 copies/mL. The mean age of HIV-infected women was 35.5 years (range, 16–55 years); 60.8% of women were African American, 17.2% were Latina, and 20.7% were white.

There were 316 cases of community-acquired bacterial pneumonia among 195 HIV-infected women (mean duration of follow-up, 4.21 years) and 13 cases among 10 HIV-uninfected women (mean duration of follow-up, 4.15 years). The rate of bacterial pneumonia among 885 HIV-infected women was 8.5 episodes/100 person-years, compared with 0.7 episodes/100 person-years among 425 HIV-uninfected women ($P < .001$).

Table 1 shows the baseline characteristics of all HIV-infected participants and of those who experienced bacterial pneumonia. Compared with white and Latina women, a higher proportion of African American women developed bacterial pneumonia. Other factors associated with bacterial pneumonia included <12 years of education, injection drug use, and cigarette smoking. The proportion of women who developed bacterial pneumonia decreased with increasing duration of HAART and/or TMP-SMX use (table 1).

Among HIV-infected women who smoked cigarettes at baseline, the rate of bacterial pneumonia was 9.8 cases/100 person-years, compared with 4.9 cases/100 person-years among persons who never smoked or who were former smokers ($P < .001$). There was no difference in the rate between former smokers and those who had never smoked. Women with injection drug use as their HIV exposure risk had a rate of bacterial pneumonia of 10.1 episodes/100 person-years, compared with 6.1 episodes/100 person-years among women with high-risk sexual behavior as an exposure risk ($P < 0.001$).

Among HIV-infected participants, there were 88 cultures yielding a bacterial pathogen for 78 (24.7%) of 316 cases of bacterial pneumonia. The predominant organism was *S. pneumoniae.* Bacteremia was documented in 34 (12.8%) of 265 blood cultures performed, and a single diagnostic organism was cultured in 52 (39.4%) of 132 purulent sputum samples and 2 (11.1%) of 18 bronchoalveolar lavage fluid specimens (table 2). There was no association between a specific organism and injection drug use.

Among 195 HIV-infected women with bacterial pneumonia, 40 (20.5%) had 2 episodes, 13 (6.7%) had 3 episodes, and 14 (7.2%) >3 episodes during follow-up. Multiple episodes were not associated with injection drug use, alcohol use, cigarette smoking, race/ethnicity, or living with children. There were 33 documented cases of PCP; there was no relationship between prior PCP and bacterial pneumonia overall or when follow-up was restricted to the period after which the $CD4^+$ lymphocyte count decreased to $\leq$200 cells/mm^3 (data not shown).

The rate of bacterial pneumonia was 17.9 episodes/100 person-years when the baseline $CD4^+$ lymphocyte count was $\leq$200 cells/mm^3, compared with 8.7 and 4.9 episodes/100 person-years when the baseline $CD4^+$ lymphocyte counts were 201–500 cells/mm^3 and >500 cells/mm^3, respectively ($P < .001$). Mean $CD4^+$ lymphocyte count at the semiannual visit before the first episode of bacterial pneumonia was 284 cells/mm^3.

Of 885 HIV-infected women, 803 (90.7%) had a $CD4^+$ lymphocyte count $\leq$500 cells/mm^3 during follow-up, of whom 587 (73.1%) were active in the study after 1 January 1996. Figure 1 stratifies these women by HAART use and displays time to first episode of bacterial pneumonia, with follow-up beginning at the first visit after 1 January 1996, at which time the $CD4^+$ lymphocyte count had decreased to $\leq$500 cells/mm^3. After 4 years of follow-up, 94% of women who used HAART for $\geq$12 months and 81% who used it for <12 months were free of bacterial pneumonia, compared with 69% of women who never used HAART ($P < .001$).

Table 3 shows factors associated with bacterial pneumonia in 658 HIV-infected women observed after 1 January 1996. The risk of bacterial pneumonia increased by 3% per year of age

Table 1. Baseline characteristics of HIV-infected study participants.

Variable	No. (%) of all HIV-infected women[a] (n = 885)	No. (%) of women with bacterial pneumonia (n = 195)	P
Race/ethnicity			
African American	538 (60.8)	137 (70.2)	.02
Latina	152 (17.2)	25 (12.8)	
White	183 (20.7)	31 (15.9)	
Other	12 (1.3)	2 (1.0)	
Education level, years			
<12	402 (45.4)	104 (53.3)	.01
⩾12	480 (54.2)	90 (46.1)	
Age at study entry, years			
<30	189 (21.3)	33 (16.9)	.12
30–40	480 (54.2)	106 (54.4)	
>40	216 (24.4)	56 (28.7)	
HIV risk history			
Injection drug use	536 (60.6)	130 (66.7)	.05
High-risk sex behavior	348 (39.3)	65 (33.3)	
Injection drug use during follow-up			
Yes	306 (34.6)	82 (42.0)	.01
No	579 (65.4)	113 (57.9)	
$CD4^+$ lymphocyte count, cells/mm^3			
>500	289 (32.6)	47 (24.1)	<.001
201–500	436 (49.3)	95 (48.7)	
⩽200	155 (17.5)	53 (27.2)	
Duration of HAART use, months[b]			
>12	141 (24.0)	7 (3.8)	<.0001
⩽12	129 (22.0)	16 (8.7)	
None	317 (54.0)	161 (87.5)	
Duration of TMP-SMX use, months[c]			
>12	149 (34.3)	26 (21.5)	.001
⩽12	138 (31.8)	42 (34.7)	
None	147 (33.9)	53 (43.8)	
Current cigarette use			
Yes	669 (75.6)	162 (83.1)	.006
No	216 (24.4)	33 (16.9)	
Daily alcohol use			
Yes	58 (6.5)	14 (7.2)	.69
No	827 (93.4)	181 (92.3)	

[a] Columns may not add up to 885 because of missing data.
[b] Limited to women with a $CD4^+$ lymphocyte count ⩽500 cells/mm^3 after 1 January 1996.
[c] Limited to women with a $CD4^+$ lymphocyte count ⩽200 cells/mm^3 during follow-up.

(adjusted hazard ratio [HR_{adj}], 1.03; 95% CI, 1.00–1.06). Women with ⩾12 years of education were more than one-third less likely to develop bacterial pneumonia than were women with <12 years of education (HR_{adj}, 0.62; 95% CI, 0.43–0.90). Current smoking doubled the risk of bacterial pneumonia (HR_{adj}, 2.12; 95% CI, 1.26–3.55). The $CD4^+$ lymphocyte count reduced the risk by 12% per increment of 50 cells (HR_{adj}, 0.88; 95% CI, 0.84–0.93). Duration of HAART and TMP-SMX use were associated with decreased risk of bacterial pneumonia; however, there was an interaction between HAART and TMP-SMX use such that the effect of HAART on bacterial pneumonia was modified by TMP-SMX use. For example, among women with 12 months of TMP-SMX use, each month of HAART use decreased the risk of bacterial pneumonia by 8% (HR_{adj}, 0.92; 95% CI, 0.89–0.95). Among women who did not receive TMP-SMX, each month of HAART use decreased the risk of bacterial pneumonia by 10% (HR_{adj}, 0.90; 95% CI, 0.86–0.94). There were no interactions between HAART use or $CD4^+$ lymphocyte

Table 2. Diagnostic culture results for HIV-infected women with bacterial pneumonia.

Finding	No. of cultures, by sample			
	All	Blood	Sputum	BAL fluid
Bacterium				
Streptococcus pneumoniae	43	25	18	0
Haemophilus influenzae	16	0	14	2
Staphylococcus aureus	22	8	14	0
Pseudomonas aeruginosa	5	1	4	0
Klebsiella pneumoniae	2	0	2	0
Total no. of positive culture results	88	34	52	2
No. of specimens without significant bacterial growth	327	231	80	16
No. of specimens cultured	415	265	132	18

NOTE. BAL, bronchoalveolar lavage.

count and viral load. Receipt of public assistance, race/ethnicity, current or former injection drug use, and study site were not significantly associated with bacterial pneumonia.

Table 3 shows the factors associated with bacterial pneumonia with follow-up starting at the first visit after 1 January 1996 in which the $CD4^+$ lymphocyte count was ≤200 cells/mm^3 (data are for 292 women). Public assistance (HR_{adj}, 0.50; 95% CI, 0.30–0.85), ≥12 years of education (HR_{adj}, 0.56; 95% CI, 0.34–0.93), and $CD4^+$ lymphocyte count per increment of 50 cells (HR_{adj}, 0.83; 95% CI, 0.72–0.95) were associated with bacterial pneumonia. The effect of HAART on bacterial pneumonia was modified by TMP-SMX use. Among women with 12 months of TMP-SMX use, each month of HAART use decreased the risk of bacterial pneumonia by 11% (HR_{adj}, 0.89; 95% CI, 0.85–0.94), whereas among women who did not receive TMP-SMX, each month of HAART use decreased the risk by 14% (HR_{adj}, 0.86; 95% CI, 0.81–0.93).

Among 68 deaths in the HER Study, 15 occurred during a hospitalization for bacterial pneumonia. The case-fatality rate for 195 HIV-infected women who developed bacterial pneumonia was 7.7%. Table 4 shows factors associated with all-cause mortality. HIV-infected women with bacterial pneumonia had a higher risk of death than did women without bacterial pneumonia (HR_{adj}, 5.02; 95% CI, 2.12–11.87), with adjustment for $CD4^+$ lymphocyte count, HAART use, and TMP-SMX use. Bacterial pneumonia was not significantly related to progression

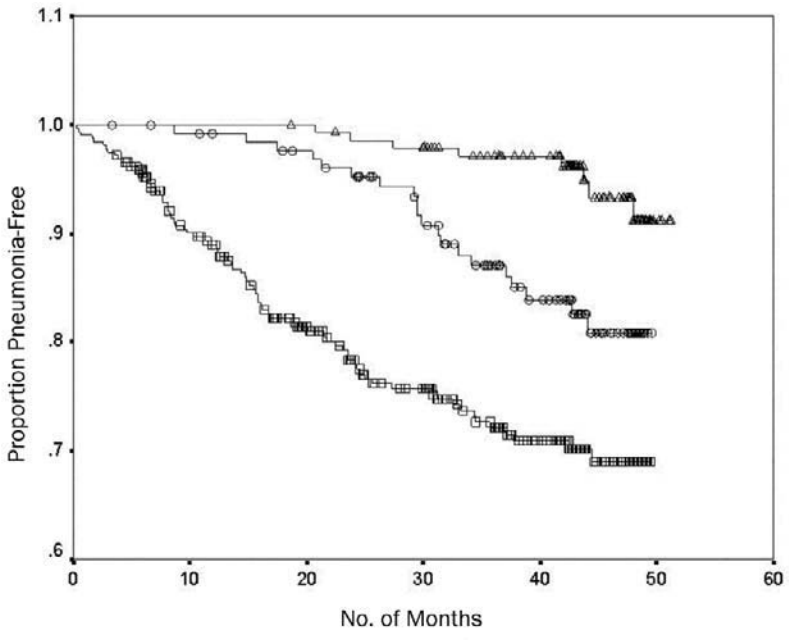

Figure 1. Pneumonia-free time among HIV-infected women with $CD4^+$ lymphocyte counts of ≤500 cells/mm^3 after 1 January 1996, stratified by HAART use. *Triangles,* HAART use for ≥12 months ($n = 141$); *circles,* HAART use for <12 months ($n = 129$); *squares,* no HAART use ($n = 317$). $P < .001$, by log-rank test for homogeneity of survival curves for the 3 groups.

Table 3. Proportional hazards models of risk factors for bacterial pneumonia among HIV-infected women limited to time since 1 January 1996.

Model, variable	HR (95% CI)	*P*
Model including 658 HIV-infected women in the HER Study after 1 January 1996		
Age	1.03 (1.00–1.06)	.03
High school education	0.62 (0.43–0.90)	.01
Cigarette smoking	2.12 (1.26–3.55)	.004
$CD4^+$ lymphocyte count (per 50 cells/mm^3)	0.88 (0.84–0.93)	<.001
Log_{10} viral load (copies/mL)	1.42 (1.16–1.72)	.0005
Duration of HAART use (in months) for persons not taking TMP-SMX[a]	0.90 (0.86–0.94)	<.001
Duration of TMP-SMX use (in months) for persons not taking HAART[a]	0.97 (0.95–0.99)	.002
Model limited to 292 HIV-infected women with a $CD4^+$ lymphocyte count ≤200 cells/mm^3		
Receipt of public assistance	0.50 (0.30–0.85)	.01
High school education	0.56 (0.34–0.93)	.03
$CD4^+$ lymphocyte count (per 50 cells/mm^3)	0.83 (0.72–0.95)	.009
Log_{10} viral load (copies/mL)	1.29 (0.96–1.74)	.09
Duration of HAART use for persons not taking TMP-SMX[a]	0.86 (0.81–0.93)	<.001
Duration of TMP-SMX use (in months) for persons not taking HAART[a]	0.96 (0.93–0.99)	.003

NOTE. HER Study, HIV Epidemiologic Research Study; HR, hazard ratio; TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] There was an interaction between HAART use and TMP-SMX use.

to clinical AIDS, excluding cases associated with AIDS-defining recurrent pneumonia.

DISCUSSION

Our study is one of few HIV prospective studies of community-acquired bacterial pneumonia in women conducted in the HAART era [13]. Our rates of pneumonia are among the highest in the literature reporting on populations in developed countries with access to HAART. Our study included women across a range of $CD4^+$ lymphocyte counts. The high rate of bacterial pneumonia is partly attributed to the fact that less than one-half of eligible women reported HAART use. However, women in the HER Study are not atypical of populations in the United States with HIV, supporting the generalizability of our data to women and drug users with HIV infection [29]. Furthermore, given that we excluded women with clinical AIDS, our rates of bacterial pneumonia are likely an underestimation.

Several studies have revealed decreasing hospitalization rates for bacterial pneumonia in the HAART era, compared with the pre-HAART era [8, 30, 31]. Tumbarello et al. [8] reported a hospitalization rate for bacterial pneumonia in Italy of 8.2 hospitalizations/100 person-years during the HAART era, similar to the rate observed in the HER Study. Our study quantified the decreased risk of pneumonia per month of HAART use at 8% per month among women with 12 months of TMP-SMX use.

Women with $CD4^+$ cell counts ≤200 cells/mm^3 were at highest risk of bacterial pneumonia (17.9 episodes/100 person-years). HAART was shown to have a stronger preventive effect for these women than when all women were considered, after adjusting for an interaction of HAART with TMP-SMX. Similar to the findings of Sullivan et al. [9], HAART use significantly reduced the risk of bacterial pneumonia in our cohort. However, unlike the study by Sullivan and colleagues, we found a significant association between TMP-SMX use and risk of bacterial pneumonia. In our study, TMP-SMX use reduced the rate of bacterial pneumonia among women who were not receiving HAART. Although early literature on the benefit of TMP-SMX treatment in preventing bacterial pneumonia has been controversial, substantial literature supports its use to prevent bacterial

Table 4. Proportional hazards model of bacterial pneumonia as a predictor of death.

Variable	HR (95% CI)	*P*
Bacterial pneumonia	5.02 (2.12–11.87)	<.001
$CD4^+$ lymphocyte count per 50 cells/mm^3	0.78 (0.68–0.89)	<.001
Duration of HAART use (in months) for persons not taking TMP-SMX[a]	0.88 (0.80–0.98)	.02
Duration of TMP-SMX use (in months) for persons not taking HAART[a]	0.94 (0.89–0.99)	.04

NOTE. HR, hazard ratio; TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] There was an interaction between HAART use and TMP-SMX use; age, education, and smoking were not found to be significant in this model.

infections, including pneumonia [14, 32–34]. The Pulmonary Complications HIV Study found that TMP-SMX treatment reduced the rate of bacterial pneumonia by 32%, but the study was conducted before the HAART era [13].

Bacterial pneumonia has been associated with an increased risk of progression to clinical AIDS [35]. We did not find a significant effect of bacterial pneumonia on progression to clinical AIDS, possibly because of a limited number of AIDS outcomes. However, bacterial pneumonia was associated with a 5-fold increased risk of death. The Pulmonary Complications HIV Study reported a shortened duration of survival associated with bacterial pneumonia, similar to that observed with PCP, despite the occurrence of bacterial pneumonia at higher $CD4^+$ lymphocyte counts [36]. These findings suggest that bacterial pneumonia behaves as an opportunistic infection and may be a cofactor for disease progression.

In the HER Study, injection drug use was not associated with bacterial pneumonia. This may be attributed to a decrease in injection drug use during the study period, given increased awareness about HIV infection and greater purity of heroin [37]. Cigarette smoking increased the risk of pneumonia >2-fold, emphasizing the need for smoking cessation programs targeted at HIV-infected persons. Lack of education was the single marker of low socioeconomic status that predicted bacterial pneumonia. This was likely an indication of suboptimal health care. Unlike other studies that have observed an increased risk of pneumococcal disease among black subjects, we found no differences in rates of pneumococcal pneumonia based on race [1, 3, 38]. *S. pneumoniae* was the predominant organism isolated, as noted in prior reports [3, 13, 35]. Furthermore, *S. pneumoniae* was implicated in ~70% of cases of bacterial pneumonia associated with bacteremia, as observed in the general population [3].

A major strength of this study is the use of medical record abstraction to confirm cases of bacterial pneumonia. However, some study limitations should be noted. HAART and TMP-SMX use was determined by self-report, and adherence was not assessed. Thus, the decreased bacterial pneumonia risk conferred by sustained adherence to HAART and TMP-SMX treatment is likely to have been underestimated. This analysis focused on bacterial pneumonia cases that resulted in hospitalization and did not include participants treated in outpatient settings, which increased specificity of diagnoses due to greater availability of microbiologic and radiographic data. Although this may have led to a bias towards more-severe cases, persons with HIV infection, pulmonary infiltrates, and fever are generally treated in the hospital. The bacterial pneumonia definitions did not include urine *Legionella* antigen tests. In addition, we cannot exclude the possibility that some cases of presumed bacterial pneumonia may have had a viral etiology. We did not include nosocomial pneumonia cases in our analysis. HAART use may have been associated with a greater reduction in the risk of bacterial pneumonia with the inclusion of nosocomial cases, given that HAART has been associated with decreased risk of hospitalization and opportunistic infections [5, 8, 12].

We did not examine the association between pneumococcal vaccination and bacterial pneumonia. Dworkin et al. [38] reported that, in the HAART era, pneumococcal vaccination of HIV-infected persons with a $CD4^+$ lymphocyte count $\geq$500 cells/ mm^3 reduced the risk of pneumococcal pneumonia. A study of HIV-infected persons in Spain observed that vaccinated participants with a baseline $CD4^+$ lymphocyte count <200 cells/mm^3 and an immunologic response to HAART experienced lower rates of bacterial pneumonia, compared with their unvaccinated counterparts, although this difference did not reach statistical significance [39]. Given the lack of consistent reports on the efficacy of pneumococcal vaccination in HIV-infected persons [40], this is an area for additional study.

In summary, HIV-infected women in the HER Study experienced high rates of bacterial pneumonia. Although HAART and TMP-SMX use decreased the rate, bacterial pneumonia was associated with an accelerated progression to death. These findings support the need for additional methods to prevent the substantial morbidity and mortality associated with bacterial pneumonia. Interventions aimed at timely initiation of HAART, TMP-SMX therapy, and smoking cessation programs are warranted.

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