

## BACTERIAL PNEUMONIA IN PERSONS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

ROBERT E. HIRSCHTICK, M.D., JEFFREY GLASSROTH, M.D., MATTHEW C. JORDAN, M.S.,  
TIMOTHY C. WILCOSKY, PH.D., JEANNE M. WALLACE, M.D., PAUL A. KVALE, M.D.,  
NORMAN MARKOWITZ, M.D., MARK J. ROSEN, M.D., BONITA T. MANGURA, M.D., PHILIP C. HOPEWELL, M.D.,  
AND THE PULMONARY COMPLICATIONS OF HIV INFECTION STUDY GROUP\*

**Abstract Background.** Patients with human immunodeficiency virus (HIV) infection are at increased risk for bacterial pneumonia in addition to opportunistic infection. However, the risk factors for bacterial pneumonia and its incidence in this population are not well defined.

**Methods.** In a multicenter, prospective, observational study, we monitored 1130 HIV-positive and 167 HIV-negative participating adults for up to 64 months for pulmonary disease. The HIV-positive group comprised 814 homosexual or bisexual men, 261 injection-drug users, and 55 female partners of HIV-infected men.

**Results.** There were 237 episodes of bacterial pneumonia among the HIV-positive participants (rate, 5.5 per 100 person-years), as compared with 6 episodes among the HIV-negative participants (rate, 0.9 per 100 person-years;  $P < 0.001$ ). The rate of bacterial pneumonia increased with decreasing CD4 lymphocyte counts (2.3,

6.8, and 10.8 episodes per 100 person-years in the strata with more than 500, 200 to 500, and fewer than 200 cells per cubic millimeter, respectively;  $P \leq 0.022$  for each comparison). Injection-drug users had a higher rate of bacterial pneumonia than did homosexual or bisexual men or female partners. In the stratum with the fewest CD4 lymphocytes, cigarette smoking was associated with an increased rate of pneumonia. Mortality was almost four times higher among participants with an episode of pneumonia than among the others. Prophylaxis with trimethoprim-sulfamethoxazole was associated with a 67 percent reduction in confirmed episodes of bacterial pneumonia ( $P = 0.007$ ).

**Conclusions.** Bacterial pneumonia is more frequent in HIV-positive persons than in seronegative controls, and the risk is highest among those with CD4 lymphocyte counts below 200 per cubic millimeter and among injection-drug users. (N Engl J Med 1995;333:845-51.)

**P**ULMONARY infections are a major cause of morbidity and mortality in persons with human immunodeficiency virus (HIV) infection.<sup>1-3</sup> Although *Pneumocystis carinii* pneumonia has received more attention, bacterial pneumonia also occurs frequently among such persons.<sup>4-6</sup> Prompt and accurate diagnosis is essential, because the outcome of HIV-associated bacterial pneumonia appears reasonably good with appropriate treatment.<sup>5,7</sup> However, the epidemiologic characteristics of bacterial pneumonia have not been well defined.<sup>7</sup> Moreover, the risk factors for bacterial pneumonia, which may be useful in developing strategies of diagnosis and management, remain largely uninvestigated.<sup>8</sup>

The Pulmonary Complications of HIV Infection Study is a multicenter, longitudinal study of HIV-seropositive persons and seronegative controls that was designed to determine the frequency, course, and outcome of pulmonary disorders in HIV-infected persons. We describe the epidemiologic features of 243 episodes

of bacterial pneumonia, 237 of which occurred in HIV-seropositive persons.

### METHODS

#### Study Population

The study participants were recruited from November 1988 through February 1990 at six centers: the University of California at San Francisco (San Francisco General Hospital), the University of California at Los Angeles (the university medical center and Olive View Hospital), Northwestern University in Chicago, Henry Ford Hospital in Detroit, Beth Israel Medical Center in New York, and the University of Medicine and Dentistry of New Jersey in Newark. Persons with the acquired immunodeficiency syndrome (AIDS), according to the 1987 definition of the Centers for Disease Control,<sup>9</sup> were excluded from the study. HIV-positive persons were recruited in two strata according to the CD4 lymphocyte count ( $\geq 400$  and  $< 400$  per cubic millimeter, with approximately equal numbers in each stratum) in three groups representing categories of HIV transmission: homosexual or bisexual men, injection-drug users, and female sexual partners of HIV-infected men. Seronegative controls were recruited from among homosexual or bisexual men and injection-drug users.

#### Study Protocol

The study protocol has been described in detail.<sup>10</sup> In brief, health-related questionnaires were completed and physical examinations, blood tests (including determinations of CD4 lymphocyte counts), chest radiography, and pulmonary-function tests were performed at entry into the study and on subsequent visits. The laboratories at each of the six study centers participated in the quality-control program of the College of American Pathologists. Participants were randomly assigned at each site to reevaluation either every three months or every six months. They were instructed to contact the study center promptly if respiratory symptoms or unexplained fever developed between scheduled visits. These symptoms triggered a diagnostic evaluation that proceeded according to specified algorithms. For example, chest radiography was performed if there was fever and a productive cough. If a focal pulmonary infiltrate was noted, sputum

From the Sections of Infectious Diseases and Pulmonary Medicine, Northwestern University, Chicago (R.E.H., J.G.); Research Triangle Institute, Research Triangle Park, N.C. (M.C.J., T.C.W.); the University of California, Los Angeles (J.M.W.); Henry Ford Hospital, Detroit (P.A.K., N.M.); Beth Israel Medical Center, New York (M.J.R.); the University of Medicine and Dentistry of New Jersey, Newark (B.T.M.); and the University of California, San Francisco (P.C.H.). Address reprint requests to Dr. Hirschtick at Northwestern University, 303 E. Superior, Passavant 828, Chicago, IL 60611.

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\*The institutions and investigators participating in the Pulmonary Complications of HIV Infection Study Group are listed in the Appendix.

samples were obtained for Gram's staining, acid-fast staining, and bacterial, fungal, and mycobacterial culture. Blood cultures were also obtained and, in general, empirical therapy for bacterial pneumonia was started pending the results of these studies.

### Diagnosis of Bacterial Pneumonia

Cases of bacterial pneumonia were classified as confirmed if there was rapid development of clinical findings compatible with that diagnosis, focal radiographic consolidation, and the isolation of a likely pathogen in a relatively pure culture or as a predominant organism from an adequate specimen of sputum ( $\geq 25$  polymorphonuclear cells and  $\leq 10$  epithelial cells per  $100\times$  field), blood, bronchoalveolar-lavage fluid, or pleural fluid. Cases were classified as presumed if there was rapid development of compatible clinical findings, focal radiographic consolidation, and the microscopic demonstration of a likely pathogen in a smear of an adequate specimen of sputum, bronchoalveolar-lavage fluid, or pleural fluid; typically, a predominant organism was noted on Gram's staining of a smear. Cases were classified as probable if there was rapid development of radiographic focal consolidation associated with fever, cough, purulent sputum, and leukocytosis that responded to antibiotic therapy.

### Statistical Analysis

Stratified analyses were used to examine the associations between the participants' base-line characteristics and the incidence of bacterial pneumonia. The variables of interest included race, sex, HIV serologic status, HIV-transmission category, CD4 lymphocyte count, cigarette-smoking status, and alcohol consumption. Race was defined as non-Hispanic white, non-Hispanic black, and other (including primarily Hispanics, with a small number of Native Americans and Asians or Pacific Islanders). There were three categories of smokers: current smokers (at entry into the study), former smokers, and non-smokers (those who had smoked fewer than 100 cigarettes in their lifetime). Alcohol consumption was dichotomized as the consumption of either less than one drink per day or one or more drinks per day on average during the month before entry into the study.

The numerators of the rate estimates were based on all episodes of bacterial pneumonia, including multiple episodes in the same person. Unless otherwise noted, the denominators were based on person-years of follow-up from entry into the study until the date of death, termination of participation in the study, or March 1994, whichever came first. The case fatality rate was calculated as the proportion of patients with bacterial pneumonia who died within four weeks after that diagnosis and in whom bacterial pneumonia was judged to be the primary cause of death.

In addition to the stratified analyses, Cox regression models of survivorship<sup>11</sup> were used to assess the independent effects of the various predictors of bacterial pneumonia. These analyses, which provided estimates of adjusted rate ratios, were based only on the first episode of bacterial pneumonia in each participant. Models that involved CD4 lymphocyte counts and the use of trimethoprim-sulfamethoxazole prophylaxis included these terms as time-dependent covariates. In the analysis of these variables, participants could move from one category to another during follow-up. Some models included episodes of bacterial pneumonia as time-dependent predictors of death. Checks of the proportional-hazards assumption using graphs indicated that the models were appropriate for these data.

Unless otherwise noted, patients in all diagnostic categories (i.e., confirmed, presumed, and probable cases of bacterial pneumonia) are represented in the analyses shown. All tests of statistical significance were two-sided. A P value of 0.05 was considered to indicate nominal statistical significance.

## RESULTS

The participants were subdivided into three strata according to their base-line CD4 lymphocyte counts: less than 200 cells per cubic millimeter (217 HIV-positive participants), 200 to 500 per cubic millimeter

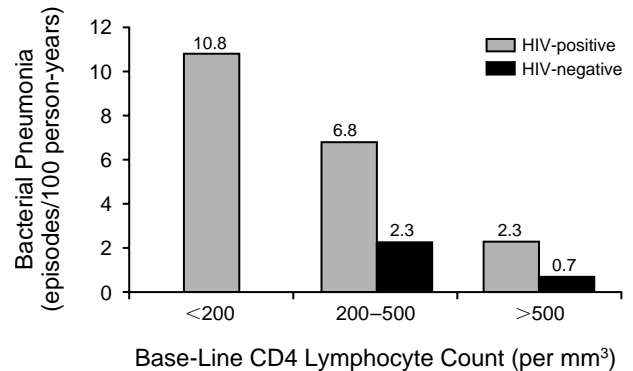


Figure 1. Rates of Bacterial Pneumonia in HIV-Seropositive and HIV-Seronegative Study Participants, According to Base-Line CD4 Lymphocyte Count.

The overall rate of pneumonia was significantly higher among HIV-positive participants than among the HIV-negative participants ( $P < 0.001$ ). Among the HIV-positive participants, the rates of pneumonia differed significantly according to the base-line CD4 lymphocyte count ( $P \leq 0.022$  for each pairwise comparison). There were no HIV-negative participants with CD4 lymphocyte counts below 200 per cubic millimeter.

(498 HIV-positive and 20 HIV-negative participants), and more than 500 per cubic millimeter (404 HIV-positive and 146 HIV-negative participants). These cutoff points were chosen to reflect clinically relevant benchmark CD4 levels. Base-line CD4 lymphocyte counts were unavailable for 11 HIV-positive participants and 1 HIV-negative participant.

The 1353 members of the cohort included 1171 HIV-seropositive and 182 HIV-seronegative participants. This analysis is based on 1130 HIV-positive participants (814 homosexual or bisexual men, 261 injection-drug users, and 55 female partners of HIV-infected men) and 167 HIV-negative participants (122 homosexual or bisexual men and 45 injection-drug users) who had at least one follow-up evaluation. During follow-up, there were 237 episodes of bacterial pneumonia in 181 HIV-positive persons. Bacterial pneumonia occurred at a higher rate in this group (5.5 cases per 100 person-years) than *P. carinii* pneumonia (221 episodes in 157 participants; rate, 5.1 per 100 person-years). The rate of bacterial pneumonia among the HIV-positive participants was significantly higher than that among the HIV-negative participants (0.9 per 100 person-years,  $P < 0.001$ ), five of whom had a total of six episodes. Even in the stratum with the highest base-line CD4 lymphocyte count (more than 500 cells per cubic millimeter), the HIV-positive participants had a significantly higher rate of pneumonia than did the HIV-negative participants ( $P = 0.004$ ) (Fig. 1). Among the HIV-infected participants, the rate of bacterial pneumonia was inversely related to the base-line CD4 lymphocyte count ( $P \leq 0.022$  for each pairwise comparison) (Fig. 1). Figure 2 shows the most recent CD4 lymphocyte count (within six months) before each participant's initial episode of bacterial pneumo-

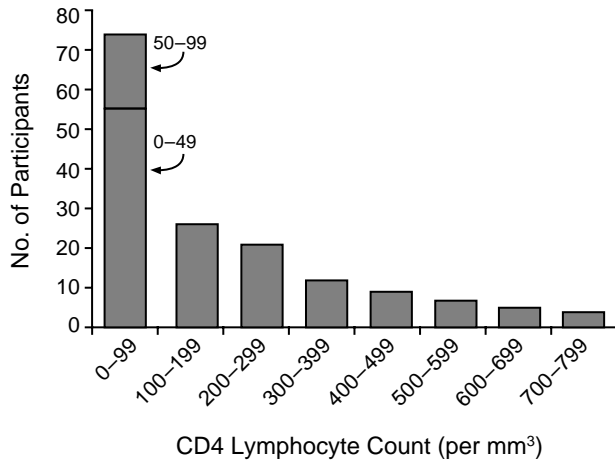


Figure 2. CD4 Lymphocyte Counts during the Six Months before the Initial Episodes of Bacterial Pneumonia in the HIV-Positive Study Participants.

The group with CD4 counts below 100 per cubic millimeter is shown subdivided into the group with 50 to 99 CD4 lymphocytes per cubic millimeter and the group with fewer than 50 CD4 lymphocytes per cubic millimeter.

nia. Although episodes occurred in all strata, they were clustered in the stratum with the lowest CD4 counts.

When univariate rate ratios of risk factors for bacterial pneumonia were derived from only the first episode of bacterial pneumonia in each participant, they were essentially the same as the ratios derived from all episodes, both initial and recurrent. Therefore, a proportional-hazards model using the time from enrollment to the first episode of bacterial pneumonia as the dependent variable was employed to describe the associations of several potential risk factors with bacterial pneumonia, after simultaneous adjustment for all independent variables. This model also showed a striking association between the occurrence of bacterial pneumonia and the CD4 lymphocyte count immediately before the initial episode of pneumonia (Table 1). The rate ratio for the risk of bacterial pneumonia was 5.7 (95 percent confidence interval, 3.5 to 9.1;  $P < 0.001$ ) for the group with counts of less than 200 per cubic millimeter, as compared with the group with counts greater than 500 per cubic millimeter.

With regard to the category of HIV transmission, the rate of bacterial pneumonia was 11.1 per 100 person-years among injection-drug users, as compared with 4.1 per 100 person-years among homosexual or bisexual men ( $P < 0.001$ ) and 3.8 per 100 person-years among female partners ( $P = 0.003$ ), on the basis of the crude (unadjusted) data. This higher rate of pneumonia in injection-drug users than in homosexual or bisexual men was observed in every stratum of the base-line CD4 lymphocyte count (Fig. 3). Among injection-drug users (the only transmission category in which a comparison between sexes was possible that

was not confounded by the transmission category itself), women had a somewhat higher rate (14.6 per 100 person-years) than men (9.0 per 100 person-years,  $P = 0.208$ ). In the proportional-hazards analysis, male injection-drug users had a rate ratio of 2.2 (95 percent confidence interval, 1.4 to 3.4;  $P = 0.001$ ) and female injection-drug users a rate ratio of 2.5 (95 percent confidence interval, 1.5 to 4.1;  $P < 0.001$ ), as compared with homosexual or bisexual men (Table 1).

The crude rate of bacterial pneumonia in whites was 4.7 per 100 person-years; in blacks it was 9.0 per 100 person-years, and in members of other races it was 2.7 per 100 person-years. However, there was probably some confounding by transmission category, because most whites in the cohort were homosexual or bisexual men, whereas most blacks were injection-drug users. No racial differences were seen within transmission categories. After direct adjustment for transmission category and sex, the rates of bacterial pneumonia were 6.2 per 100 person-years for whites (95 percent confidence interval, 5.0 to 7.4), 6.6 per 100 person-years for blacks (95 percent confidence interval, 4.6 to 8.5), and 2.9 per 100 person-years for members of other races (95 percent confidence interval, 1.0 to 4.8). The rate ratios derived from the proportional-hazards model, which were also adjusted for several additional variables, were not statistically significant with regard to race (Table 1).

The rates of bacterial pneumonia according to smoking status were also subject to confounding by transmission category. The crude rate for smokers was 7.3 per 100 person-years, as compared with 3.5 per 100 person-years for nonsmokers ( $P < 0.001$ ). The differ-

Table 1. Adjusted Rate Ratios for Bacterial Pneumonia among the HIV-Seropositive Study Participants.\*

| VARIABLE                         | RATE RATIO (95% CI) | P VALUE      |         |
|----------------------------------|---------------------|--------------|---------|
|                                  |                     | FOR CATEGORY | OVERALL |
| CD4 lymphocytes/mm <sup>3</sup>  |                     |              | <0.001  |
| >500                             | 1.0                 | —            |         |
| 200–500                          | 1.5 (0.92–2.6)      | 0.099        |         |
| <200                             | 5.7 (3.5–9.1)       | <0.001       |         |
| Transmission category            |                     |              | 0.001   |
| Homosexual or bisexual men       | 1.0                 | —            |         |
| Injection-drug users             |                     |              |         |
| Male                             | 2.2 (1.4–3.4)       | 0.001        |         |
| Female                           | 2.5 (1.5–4.1)       | <0.001       |         |
| Female partners                  | 0.99 (0.43–2.3)     | 0.977        |         |
| Race                             |                     |              | 0.151   |
| White                            | 1.0                 | —            |         |
| Black                            | 0.94 (0.63–1.4)     | 0.754        |         |
| Other                            | 0.49 (0.24–1.0)     | 0.052        |         |
| Smoking status                   |                     |              | 0.180   |
| Never smoked                     | 1.0                 | —            |         |
| Former smoker                    | 0.91 (0.54–1.5)     | 0.733        |         |
| Current smoker                   | 1.3 (0.91–1.9)      | 0.144        |         |
| Alcohol consumption (drinks/day) |                     |              | 0.564   |
| ≤1                               | 1.0                 | —            |         |
| >1                               | 0.90 (0.63–1.3)     | 0.564        |         |

\*The CD4 lymphocyte counts used in this analysis were time-dependent covariates. All other variables are base-line characteristics. The first category listed for each variable is the reference category. CI denotes confidence interval.

ence was more marked in the stratum with fewer than 200 CD4 lymphocytes per cubic millimeter (14.1 per 100 person-years among smokers vs. 5.4 per 100 person-years among nonsmokers,  $P=0.003$ ). However, there was substantial overlap between injection-drug users and smokers. The direct rate of bacterial pneumonia, after adjustment for transmission category, was 3.9 per 100 person-years among nonsmokers (95 percent confidence interval, 2.5 to 5.3), 4.8 per 100 person-years among former smokers (95 percent confidence interval, 2.3 to 7.4), and 6.5 per 100 person-years among current smokers (95 percent confidence interval, 5.5 to 7.5). The adjusted rate ratios for the proportional-hazards model were not significant (Table 1). However, in participants with fewer than 200 CD4 lymphocytes per cubic millimeter at entry into the study, the adjusted rates of bacterial pneumonia were 4.0 per 100 person-years (95 percent confidence interval, 1.7 to 6.3) among nonsmokers and 13.8 per 100 person-years (95 percent confidence interval, 9.9 to 17.7) among current smokers ( $P<0.05$ ).

The alcohol consumption reported by participants was unrelated to the rate of bacterial pneumonia in both the analysis of crude data and the proportional-hazards analysis (Table 1).

At least one organism was identified in 92 of 237 episodes of bacterial pneumonia (38.8 percent) in the HIV-positive participants. Thirteen of these episodes involved unlikely pathogens (Table 2) and were therefore classified as probable cases. There were 79 confirmed, 19 presumed, and 139 probable episodes. The organisms identified most commonly were *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*. Multiple bacteria were identified in nine episodes, for a total of 89 bacterial isolates (Table 2).

The estimated case fatality rate (i.e., the mortality attributed to bacterial pneumonia) among all episodes was 6 percent. A proportional-hazards model that included bacterial pneumonia and CD4 lymphocyte count as time-dependent variables, sex and HIV-trans-

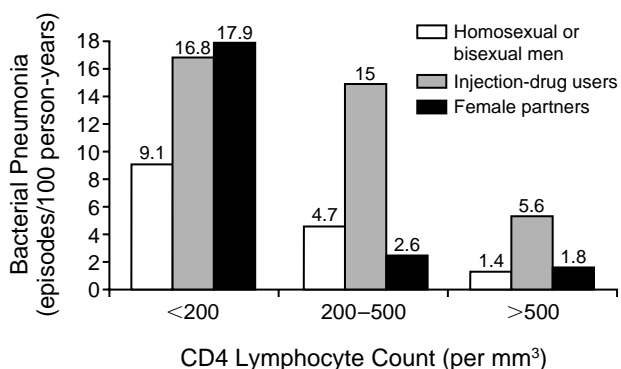


Figure 3. Rates of Bacterial Pneumonia in Relation to CD4 Lymphocyte Counts and HIV-Transmission Categories.

In each stratum of the CD4 lymphocyte count, injection-drug users had a higher rate of bacterial pneumonia than homosexual or bisexual men.

Table 2. Organisms Cultured from the Study Participants with Bacterial Pneumonia.\*

| ORGANISM                        | TYPE OF SAMPLE CULTURED |        |               |       |               |
|---------------------------------|-------------------------|--------|---------------|-------|---------------|
|                                 | ALL                     | SPUTUM | LAVAGE FLUID† | BLOOD | PLEURAL FLUID |
| <i>Streptococcus pneumoniae</i> | 36                      | 21     | 3             | 11    | 1             |
| <i>Staphylococcus aureus</i>    | 13                      | 7      | 4             | 2     | —             |
| <i>Haemophilus influenzae</i>   | 12                      | 9      | 2             | 1     | —             |
| <i>Klebsiella pneumoniae</i>    | 10                      | 7      | 2             | 1     | —             |
| <i>Pseudomonas aeruginosa</i>   | 6                       | 6      | —             | —     | —             |
| <i>Escherichia coli</i>         | 3                       | 3      | —             | —     | —             |
| <i>Serratia marcescens</i>      | 3                       | 2      | 1             | —     | —             |
| Other‡                          | 6                       | 5      | 0             | 1     | 0             |
| All                             | 89                      | 60     | 12            | 16    | 1             |
| No. of specimens cultured       | 252                     | 148    | 27            | 73    | 4             |

\*The following organisms were cultured but were considered unlikely to be pathogens in the study participants: haemophilus species (cultured from sputum samples from four participants); coagulase-negative staphylococci (from sputum samples from four participants and from blood and bronchoalveolar-lavage fluid from one participant each); and clostridium species, *Prevotella melaninogenica*, alpha-hemolytic streptococci, and bacillus species (from samples of bronchoalveolar-lavage fluid from one participant each).

†Denotes bronchoalveolar-lavage fluid.

‡*Legionella pneumophila*, *Moraxella catarrhalis*, *Nocardia asteroides*, *Proteus mirabilis*, and proteus species were found in one sputum sample each, and *Pasteurella multocida* was found in one blood sample.

mission category as independent variables, and time to death (from any cause) as the dependent variable was used to evaluate bacterial pneumonia as a predictor of mortality. The mortality rate ratio was 3.9 (95 percent confidence interval, 3.1 to 5.0;  $P<0.001$ ) among participants who had any bacterial pneumonia, as compared with participants who did not.

Proportional-hazards analysis was also used to examine the relation between the use of trimethoprim-sulfamethoxazole as prophylaxis against *P. carinii* pneumonia and the rate of bacterial pneumonia. In this analysis, follow-up was limited to person-years with CD4 lymphocyte counts below 200 per cubic millimeter. Although prophylactic trimethoprim-sulfamethoxazole was not given in a uniform dose within the cohort, it was most often given three times weekly. A total of 403 participants received prophylactic trimethoprim-sulfamethoxazole during the follow-up period. After adjustment for transmission category and sex, the model indicated that this prophylaxis reduced the risk of bacterial pneumonia by 32 percent (rate ratio, 0.68; 95 percent confidence interval, 0.44 to 1.0;  $P=0.08$ ). When only episodes of confirmed bacterial pneumonia were considered, trimethoprim-sulfamethoxazole reduced the risk of bacterial pneumonia by 67 percent (rate ratio, 0.33; 95 percent confidence interval, 0.14 to 0.73;  $P=0.007$ ).

These analyses are based on all cases of bacterial pneumonia, confirmed, presumed, and probable. Except as noted, consistent associations were found when the analyses were limited to the confirmed cases.

## DISCUSSION

Early in the HIV epidemic, it was observed that bacterial pneumonia was a common cause of hospitalization among homosexual men with AIDS.<sup>4</sup> Subsequent

reports suggested that bacterial pneumonia was more frequent in HIV-positive persons than in the population at large.<sup>5,6</sup> Additional reports noted a particularly high incidence of this type of pneumonia in HIV-infected injection-drug users.<sup>12-15</sup> However, these reports were based on studies that were retrospective, were conducted at single institutions, described populations lacking racial and ethnic diversity, or included only persons from a single HIV-transmission category, making it difficult to extend the results to the HIV-infected population at large. Our report is based on a large, multicenter cohort representative of the major groups at risk for HIV transmission in the United States, a cohort that was followed prospectively for 64 months.

Bacterial pneumonia occurred frequently in the cohort, more often than did *P. carinii* pneumonia, although it should be noted that many patients were receiving prophylaxis against *P. carinii* pneumonia. Both types of pneumonia were less frequent than acute bronchitis, the most common disorder of the lower respiratory tract in the cohort.<sup>16</sup>

The most striking result of this analysis was the association between the occurrence of bacterial pneumonia and reduced CD4 lymphocyte counts. Although bacterial pneumonia occurred with virtually all CD4 lymphocyte counts, approximately one third of initial episodes occurred in persons with fewer than 50 CD4 lymphocytes per cubic millimeter, and approximately two thirds occurred in persons with fewer than 200 CD4 lymphocytes per cubic millimeter. The associations between reduced CD4 lymphocyte counts and *P. carinii* pneumonia,<sup>17</sup> cytomegalovirus retinitis,<sup>18</sup> and disseminated *Mycobacterium avium* complex<sup>19</sup> have been established previously. Until now, a similar association between reduced CD4 lymphocyte counts and bacterial pneumonia has been reported only in HIV-infected injection-drug users.<sup>13,20</sup> The data from our cohort extend this observation to a broader group of persons in a variety of HIV-transmission categories and serve to remind clinicians that not all infections of the respiratory tract in advanced HIV disease are due to opportunistic organisms.

Although primarily a disorder of cell-mediated immunity, HIV infection is associated with substantial dysfunction of humoral immunity.<sup>21-23</sup> It predisposes patients to bacterial infections, particularly with encapsulated organisms such as *S. pneumoniae* and *H. influenzae*.<sup>22-24</sup> Polyclonal hypergammaglobulinemia, impaired B-cell activation, and impaired local pulmonary defenses are common.<sup>21-23,25,26</sup> CD4 lymphocytes regulate B-cell differentiation and play an indirect part in the production of antibodies and phagocytosis.<sup>25</sup> The increased rate of bacterial pneumonia in study participants with fewer than 200 CD4 lymphocytes per cubic millimeter is therefore not surprising. However, HIV-positive participants with fewer than 500 CD4 lymphocytes per cubic millimeter also had significantly more episodes of bacterial pneumonia than did HIV-nega-

tive participants with similar counts, suggesting that immune dysfunction occurs even with a minimal reduction in the CD4 lymphocyte count.

The incidence of bacterial pneumonia in injection-drug users was substantially higher than that in homosexual or bisexual men, in all three lymphocyte-count strata. Injection-drug users without HIV infection have been noted to be at increased risk for bacterial pneumonia.<sup>27,28</sup> HIV infection appears to heighten that risk. Selwyn et al.<sup>12</sup> reported a higher rate of bacterial pneumonia among HIV-seropositive injection-drug users than among seronegative injection-drug users. Among HIV-infected patients, Witt et al.<sup>6</sup> reported a higher incidence of bacterial infections, including pneumonia, in injection-drug users than in homosexual men. Data from our cohort confirm this association.

The microbiologic cause of bacterial pneumonia identified most frequently in our cohort was *S. pneumoniae*. Earlier reports noted the frequency of this organism in HIV-associated pneumonia.<sup>4,7,12-14,29</sup> *S. pneumoniae* has also been identified in several large series as the most common cause of pneumonia in the general population.<sup>30-33</sup> The fact that no etiologic organism was identified in a substantial number of episodes is consistent with reports of pneumonia in the general population.<sup>30-33</sup>

Cigarette smoking has been associated with an increased risk of *P. carinii* pneumonia and progression to AIDS,<sup>34,35</sup> although this association has been disputed.<sup>36</sup> Smoking has not been linked with bacterial pneumonia in HIV infection.<sup>20</sup> We found no statistically significant association between smoking and the rate of bacterial pneumonia, after adjustment for transmission category. However, in participants with fewer than 200 CD4 lymphocytes per cubic millimeter at base line, there was an increased rate of bacterial pneumonia among the smokers. Given the high rate of bacterial pneumonia in this group, anyone with a CD4 lymphocyte count below 200 per cubic millimeter should be advised to stop smoking.

Hardy et al.<sup>37</sup> have reported a lower incidence of bacterial infections, including pneumonia, among patients receiving trimethoprim-sulfamethoxazole as prophylaxis against *P. carinii* pneumonia than among those receiving aerosolized pentamidine. Our study confirms a reduced incidence of bacterial pneumonia among patients receiving trimethoprim-sulfamethoxazole. Because exact dates of trimethoprim-sulfamethoxazole use were not always available, there may have been some misclassification of this use before the onset of bacterial pneumonia. Such nondifferential misclassification typically causes a conservative bias in simple stratified analyses.<sup>38</sup> In addition, clinicians may have been more vigilant in monitoring patients at risk for bacterial pneumonia. The true protective effect of trimethoprim-sulfamethoxazole may therefore have been underestimated in this analysis. Trimethoprim-sulfamethoxazole is currently considered the agent of choice for prophylaxis against *P. carinii* pneumonia<sup>37,39,40</sup> and

perhaps against toxoplasmosis<sup>37,41</sup> in HIV-infected persons at risk. Protection against bacterial pneumonia should also be included among its benefits.

These results have several important messages for clinicians. Among HIV-infected persons, bacterial pneumonia occurs with increased frequency at all CD4 lymphocyte counts, but it is substantially more frequent among those with fewer than 200 CD4 lymphocytes per cubic millimeter. Bacterial pneumonia is particularly frequent among injection-drug users. Smokers, especially those with low CD4 lymphocyte counts, are also at increased risk. Differential diagnosis and clinical management should reflect these findings. Among the strategies for dealing with persons at risk, smoking cessation and the use of trimethoprim-sulfamethoxazole as prophylaxis against *P. carinii* pneumonia should be considered because of their potential benefits with regard to bacterial pneumonia, and possibly mortality.

#### APPENDIX

The following institutions and investigators participated in the Pulmonary Complications of HIV Infection Study Group:

*University of California, San Francisco:* P.C. Hopewell (principal investigator and Steering Committee chairman), J. Stansell, J. Turner, D. Osmond, and C. Merrifield; *Northwestern University, Chicago:* J. Glassroth (principal investigator and Steering Committee vice chairman), M. Mossar, and R. Hirschtick; *Beth Israel Medical Center, New York:* M.J. Rosen (principal investigator), L. Meiselman, K.J. Manghisi, and R.F. Schneider; *University of Medicine and Dentistry of New Jersey-New Jersey Medical School, University Hospital, Newark:* L.B. Reichman (principal investigator), B. Mangura, and S. Barnes; *University of California, Los Angeles:* J.M. Wallace (principal investigator), B. Richer, J. Au, A. Coulson, and V. Clemente; and *Henry Ford Hospital, Detroit:* P.A. Kvale (principal investigator), N. Markowitz, L.D. Saravolatz, C. Johnson, J. Huitsing, and A. Krystoforski; *Coordinating Center (Research Triangle Institute, Research Triangle Park, N.C.):* W.K. Poole (principal investigator), A.V. Rao, K. Clayton, N. Hanson, M. Jordan, J. Thompson, D. Myers, L. LaVange, J. Katzin, W. Fulkerson, T. Wilcosky, and Y. Lou.

*National Heart, Lung, and Blood Institute, Bethesda, Md.:* A.R. Kalica, J. Wittes, and D. Follmann.

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