

# HIV-related *Pneumocystis carinii* Pneumonia in Older Patients Hospitalized in the Early HAART Era

Benjamin Kim, BA, Thomas M. Lyons, PhD, Jorge P. Parada, MD, MPH, Constance R. Uphold, PhD, ARNP, RN, Paul R. Yarnold, PhD, Jennie B. Hounshell, BA, Alison M. Sipler, BA, Matthew B. Goetz, MD, Jack A. DeHovitz, MD, MPH, Robert A. Weinstein, MD, Rafael E. Campo, MD, Charles L. Bennett, MD, PhD

**OBJECTIVE:** To determine whether older age continues to influence patterns of care and in-hospital mortality for hospitalized persons with HIV-related *Pneumocystis carinii* pneumonia (PCP), as determined in our prior study from the 1980s.

**DESIGN:** Retrospective chart review.

**PATIENTS/SETTING:** Patients (1,861) with HIV-related PCP at 78 hospitals in 8 cities from 1995 to 1997.

**MEASUREMENTS:** Medical record notation of possible HIV infection; alveolar-arterial oxygen gradient; CD4 lymphocyte count; presence or absence of wasting; timely use of anti-PCP medications; in-hospital mortality.

**MAIN RESULTS:** Compared to younger patients, patients  $\geq 50$  years of age were less likely to have HIV mentioned in their progress notes (70% vs 82%,  $P < .001$ ), have mild or moderately severe PCP cases at admission (89% vs 96%,  $P < .002$ ), receive anti-PCP medications within the first 2 days of hospitalization (86% vs 93%,  $P < .002$ ), and survive hospitalization (82% vs 90%,  $P < .003$ ). However, age was not a significant predictor of mortality after adjustment for severity of PCP and timeliness of therapy.

**CONCLUSIONS:** While inpatient PCP mortality has improved by 50% in the past decade, 2-fold age-related mortality differences persist. As in the 1980s, these differences are associated with lower rates of recognition of HIV, increased severity of illness at admission, and delays in initiation of PCP-specific treatments among older individuals—factors suggestive of delayed recognition of HIV infection, pneumonia, and PCP, respectively. Continued vigilance for the possibility of HIV and HIV-related PCP among persons  $\geq 50$

years of age who present with new pulmonary symptoms should be encouraged.

**KEY WORDS:** HIV; *Pneumocystis carinii* pneumonia; age; quality of care; outcomes.

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The Centers for Disease Control and Prevention (CDC) reports that 5% of HIV infection cases in the United States through December 1999 were diagnosed in persons 50 years of age or older, and the percentage of AIDS cases diagnosed in this age group has remained at about 10% since 1991.<sup>1,2</sup> However, health care workers and the public alike tend not to perceive HIV infection as a disease affecting older patients. A 1996 survey found that primary care physicians rarely discussed HIV/AIDS or HIV-related risk factor reduction with older patients and that older patients rarely asked questions concerning HIV or AIDS.<sup>3</sup> Asymptomatic older HIV-infected individuals are less likely to seek out testing and medical care.<sup>4</sup> Symptomatic older HIV-infected individuals are more likely to attribute HIV-related symptoms to other illnesses or to the normal aging process.<sup>4</sup> Consequently, HIV infection in older patients may not be recognized until late in the course of the disease. The CDC estimates suggest that a higher proportion of older HIV-infected individuals present with an AIDS-defining opportunistic illness (OI) and die within the same month of being diagnosed with AIDS than younger HIV-infected persons.<sup>2</sup> Deaths due to HIV infection may also go unrecognized in older individuals. Researchers at a Harlem, NY, hospital examined a sample of deceased patients without known HIV diagnosis and found a 6% rate of HIV infection in anonymous blood samples from older, deceased males and a 9% rate of HIV infection in older, deceased females.<sup>5</sup>

Although the use of prophylaxis and highly active antiretroviral therapy (HAART) has reduced the incidence of AIDS-defining OIs among HIV-infected patients, *Pneumocystis carinii* pneumonia (PCP) still remains an important OI. CDC surveillance from 1992 to 1997 indicates that PCP continued to be the most common presenting AIDS-defining OI.<sup>6</sup> AIDS-defining OIs such as PCP are more likely to occur in patients who are considered unlikely to be HIV-infected or for whom access to HIV care occurs late in the disease course, as may be the case with many older, HIV-infected patients.<sup>6</sup>

Using data from 2,174 HIV-related PCP cases diagnosed between 1987 and 1990, we previously reported that patients  $\geq 50$  years of age were 10% less likely to have HIV

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Received from the Department of Medicine, Northwestern University Medical School, Chicago, Ill (BK, TML, PRY, JBH, AMS, CLB); the Stricht School of Medicine—Loyola University, Maywood, Ill, and the Midwest Center for Health Services Research and Policy, Hines VA Hospital, Hines, Ill (JPP); the Brain Rehabilitation Research Center, Malcolm Randall VA Medical Center, Gainesville, Fla (CRU); the Department of Medicine, VA Greater Los Angeles Healthcare System and the UCLA School of Medicine, Los Angeles, Calif (MBG); the Department of Medicine, SUNY Health Science Center at Brooklyn, Brooklyn, NY (JAD); the Department of Medicine, Cook County Hospital and Rush Medical College, Chicago, Ill (RAW); the Division of Infectious Diseases, University of Miami School of Medicine, Miami, Fla (REC); and the VA Chicago Health Care System—Lakeside Division, Chicago, Ill (CLB).

Address correspondence and reprint requests to Dr. Bennett: VA Chicago Health Care System—Lakeside Division, 400 E. Ontario St., Suite 205, Chicago, IL 60611 (e-mail: cbenne@northwestern.edu).

noted in their progress notes, 15% less likely to present with mild or moderately severe cases of PCP, 11% less likely to receive timely PCP-specific therapy, and almost twice as likely to die in-hospital compared to younger patients.<sup>7</sup> A decade later, overall care for PCP has improved dramatically, with inpatient mortality rates decreasing from 18% in the late 1980s to 11% during the years 1995 to 1997.<sup>7,8</sup> In light of the overall improvements in PCP care and outcomes, we evaluate whether age-related differences in severity of illness at admission, PCP-related patterns of care, and survival still persist.

## METHODS

### Sampling of Cities, Hospitals, and Patients

This cross-sectional study analyzes the care processes and outcomes of 1,861 HIV-infected patients who received care for PCP in New York, NY; Chicago, Ill; Los Angeles, Calif; Miami, Fla; Seattle, Wash; Phoenix, Ariz; Nashville, Tenn; and Memphis, Tenn, from 1995 to 1997. These cities represent 4 high AIDS-incidence and 4 intermediate-to-low AIDS-incidence regions, geographically dispersed across the United States.

The sampling method for hospitals and patients has been described in detail previously.<sup>8</sup> In each city, a random sample of non-Veterans Affairs hospitals was chosen for inclusion in the study. Seventy-eight hospitals, representing >90% of hospitals chosen for the study, agreed to participate. Hospitals differed in ownership, teaching affiliation, and prior experience with AIDS patients. From each hospital, a random sample of HIV-infected PCP patients was selected. The number of charts reviewed from each hospital was approximately proportional to that hospital's caseload.

All medical records with International Classification of Diseases, 9th Revision, Clinical Modification codes for PCP (136.3) and HIV-related disease (042–044) between January 1, 1995, and December 31, 1997, were screened for inclusion in the study. Eligibility criteria required that patients be 18 years of age or older and have cytologic confirmation of PCP or physician notes indicating that PCP accounted for the pulmonary process. Patients were excluded if they had received medical care for the current PCP episode at another hospital, were admitted for other conditions or only for diagnostic bronchoscopy, or had a diagnosis of cancer (except Kaposi's sarcoma) reported in either the admitting note or discharge sheet.

### Data Acquisition and Quality

Information from 1,861 medical records was included in this study. In each city, trained registered nurses having experience with AIDS and utilization review were recruited as medical records abstractors. Data quality was ensured by periodic evaluation of abstracted data by a study physician. Inter-rater reliability was evaluated by reabstraction of 5% of the records by a different abstractor.

Greater than 95% concordance was observed regarding sociodemographic characteristics, severity of illness, process of care, and outcomes.

### Study Variables

**Patient Characteristics.** Patients were characterized by age, gender, race, HIV-related risk factor, insurance status, and prior HIV-related care. Age at hospital admission was measured as a continuous variable using date of birth or was recorded directly from the medical record. As in previous HIV-related age studies, patients aged 50 years or older constituted the older age group.<sup>2,7,9</sup> Race was categorized as white, African American, or Hispanic/other. HIV-related risk factors were categorized according to information included in the medical records and included the following hierarchically ordered groups: men who have sex with men (MSM), patients reporting injection drug use, patients reporting noninjection drug use, and patients with unknown or unreported risk factors. Heterosexual acquisition of HIV-infection was infrequently noted in the medical records. Insurance status was categorized as private insurance (including fee-for-service and preferred provider organizations), public insurance (including Medicaid, Medicare, and government-sponsored veterans insurance), and self-pay/no insurance. Prior HIV-related care included prior antiretroviral and PCP prophylaxis use.

**Severity of Illness.** Alveolar-arterial oxygen gradient was categorized as  $\leq 48.5$  mm Hg and  $>48.5$  mm Hg. CD4 lymphocyte counts were classified as  $<50$  cells/mm<sup>3</sup>, 50–200 cells/mm<sup>3</sup>, or  $>200$  cells/mm<sup>3</sup>, based on information on CD4 count measurements obtained within 3 months prior to admission. Low rates of recording of actual CD4 lymphocyte counts limited our ability to evaluate a continuous versus categorical measure for this variable. Severity of illness (SOI) at admission was categorized using a recently developed PCP-specific staging system based on three factors.<sup>8</sup> Stage 1 included patients with no evidence of wasting (operationally defined as documentation of weight loss  $>20\%$  and/or wasting syndrome) and an alveolar-arterial oxygen gradient  $\leq 53$  mm Hg and had an associated mortality rate of 3.7%. Stage 2 included patients with wasting and an alveolar-arterial oxygen gradient  $\leq 53$  mm Hg and had an associated mortality rate of 8.5%. Stage 3 included patients with no evidence of wasting and an alveolar-arterial oxygen gradient  $>53$  mm Hg and had an associated mortality rate of 16.1%. Stage 4 included patients with an alveolar-arterial oxygen gradient  $>53$  mm Hg, evidence of wasting, and a serum albumin level  $>2.55$  g/dl and had an associated mortality rate of 23.3%. Stage 5 included patients with an alveolar-arterial oxygen gradient  $>53$  mm Hg, evidence of wasting, and a serum albumin  $\leq 2.55$  g/dl and had an associated mortality rate of 49.1%. In comparison to the previously derived severity of PCP model for the years 1987 to 1990, this model performed 52% better.<sup>10</sup>

**Comorbid Diseases and Neurologic Examination.** Presence of comorbidity was defined as a history of diabetes mellitus, renal disease, liver disease, chronic obstructive pulmonary disease, emphysema, asthma, or chronic bronchitis. Neurologic conditions were defined as comatose, confusion, or neurologic symptoms in the first two days mentioned in the physician notes.

**Process of Care and Outcomes.** The timing and intensity of the care were evaluated based on the treatment and outcome of the PCP episode. The selected measures were derived from input from expert consultants who identified process measures that were likely to be associated with good outcomes (survival).<sup>11</sup> Three important process measures were identified a priori: timely recognition of HIV infection, pneumonia, and PCP. For HIV, we evaluated medical records for the presence/absence of timely entries noting possible HIV infection. For pneumonia, we evaluated severity of PCP at the time of admission, because individuals whose PCP was not previously suspected might be more likely to present with severe cases of PCP. For treatment measures, we examined the timely use of anti-PCP medications—defined as trimethoprim/sulfamethoxazole, dapsone, trimetrexate, pentamidine isethionate, clindamycin/primaquine, pyrimethamine, and atovaquone—within 2 days of admission, because patients who were not recognized as probably having PCP might be less likely to receive timely and appropriate therapy for PCP. Our prior review of PCP cases from 1987 to 1990 found that survival rates were highest for PCP patients with HIV infection noted in the medical records, low severity of PCP infection, and anti-PCP medications initiated within 2 days of admission.<sup>7</sup> We also evaluated the timely use of adjunctive corticosteroids within 3 days of initiation of anti-PCP medications, based on the recommendations from the 1990 NIH consensus statement on this subject.<sup>12</sup> We also analyzed direct measures of resource use, such as ICU utilization, intubation, and ER admission. Outcome was defined by discharge status (alive or dead). Length of stay (LOS) was measured in days and included only patients who were alive upon discharge.

**Hospital Characteristics.** Hospitals were characterized according to teaching status (non-teaching versus teaching) and ownership (church-affiliated/not-for-profit, county/state, versus private for-profit), as documented in the American Hospital Association guide.<sup>13</sup> Hospital experience was characterized by the total number of HIV-related PCP patients cared for between the years 1995 and 1997 (low, <35 cases; high, ≥35 cases), as described in prior studies.<sup>8,14,15</sup>

## Confidentiality

Patient, physician, and hospital confidentiality was maintained throughout the study. Institutional Review

Board approval was obtained from each study hospital prior to initiation of data collection.

## Statistical Analysis

Data analysis proceeded in 2 stages. First, bivariate analysis was used to compare patient variables by age. Age was treated as a dichotomous variable (age <50 versus age = 50), as in our prior study of age-related variations in PCP care.<sup>7</sup> The analysis was repeated using an age 60 cutoff, and the results were similar to those reported. The  $\chi^2$  test or Fisher's exact test was used as appropriate. Then, logistic regression analyses were conducted to determine if independent care process and severity of illness measures were predictors of mortality and to test the hypothesis that older age did not correlate with higher mortality rates after controlling for these independent predictors. A 2-sided *P* value < .05 was considered statistically significant. With the dependent variable being in-hospital survival, the first logistic model included age and severity of illness score. The second logistic model included age, severity score, timely PCP medications (within 48 hours of admission), and timely steroids given (within 72 hours of initiation of PCP therapy). Other potential independent predictors of mortality, such as neurologic change, were not entered into a logistic model because they were not significantly different for older versus younger patients in bivariate analyses. We also investigated the possibility of a significant age by comorbidity interaction in the multivariate mortality analyses. The results were similar, suggesting that an age-comorbidity interaction was not present in this study.

## RESULTS

### Patient Characteristics

Of the 1,861 study patients, 164 (9%) were ≥50 years old. Older patients were less likely to be identified as a homosexual or bisexual male (17.1% vs 30.6%, *P* < .001) but were similar to younger patients with respect to distributions according to gender, race/ethnicity, and type of health insurance coverage (Table 1). While rates of prior antiretroviral use were similar for older and younger patients, older patients were 11% less likely to have previously received PCP prophylaxis (37.2% vs 48.3%, *P* < .008).

### Severity of Illness/Comorbidity

Severity of illness differed between patients ≥50 years of age and younger patients. Older patients were more likely to have an alveolar-arterial oxygen gradient >48.5 mm Hg (56.1% vs 42.6%, *P* < .004) and to have a grade 5 PCP severity of illness stage (11.4% vs 4.3%, *P* < .002), but they were also less likely to be severely immune compromised, with one-third more of the older patients having a CD4 lymphocyte count ≥50 cells/mm<sup>3</sup> (55.4% vs 38.7%,

Table 1. Age Differences in Patient and Hospital Variables

Variable	Age <50, % (N = 1,697)	Age ≥50, % (N = 164)	P Value
Patient characteristics			
Gender			
Male	81.1	87.2	.071
Female	18.9	12.8	
Race			
White	38.5	37.2	.870
African American	37.7	37.2	
Hispanic	23.8	25.6	
Risk factor			
MSM*	30.6	17.1	.001
IVDU†	17.4	17.1	
Users of non-IV drugs	13.3	9.2	
Other/none	38.7	56.7	
Insurance			
Public	49.7	48.8	.142
Self-pay/none	27.8	22.6	
Private	22.6	28.7	
Prior HIV-related care			
Prior antiretroviral use	33.6	28.1	.176
Prior PCP prophylaxis	48.3	37.2	.008
Prior protease inhibitor use	9.2	8.0	.617
Severity of illness			
Albumin			
≤2.55 g/dl	22.4	25.6	.400
>2.55 g/dl	77.6	74.4	
A-a O <sub>2</sub> gradient			
≤48.5 mm Hg	57.4	43.9	.004
>48.5 mm Hg	42.6	56.1	
Wasting			
No	71.9	66.3	.156
Yes	28.2	33.7	
Severity score			
Stage 1	48.8	37.9	.002
Stage 2	16.5	13.6	
Stage 3	25.4	30.3	
Stage 4	5.0	6.8	
Stage 5	4.3	11.4	
CD4 lymphocyte count‡			
<50	61.3	44.6	.014
50–200	27.3	45.8	
>200	11.4	9.6	
Presence of comorbidity	41.9	42.7	.911
Neurologic change	10.7	15.9	.063
Process of care and outcomes			
Timely PCP medication	92.9	85.8	.002
Timely steroid use	50.1	58.4	.054
ICU utilization	12.8	22.0	.002
Intubation	8.4	14.6	.012
ER admission	70.7	74.4	.359
HIV noted in MD progress notes	82.3	69.5	.001
Length of stay, d, mean§	10.3	12.4	.027
Hospital characteristics			
Hospital teaching status			
Nonteaching	41.4	34.8	.118
Teaching	58.6	65.2	
Hospital ownership			
Church/non-for-profit	62.1	62.8	.806
County/state	26.3	24.4	
Private for-profit	11.6	12.8	
AIDS experience of hospital			
Low	15.6	17.1	.691
High	84.4	82.9	
Outcome			
Mortality	10.4	18.3	.003

\* MSM, men who have sex with men.

† IVDU, intravenous drug user.

‡ Wilcoxon test.

§ Student t test.

$P < .014$ ). There were no significant differences in the presence of a comorbid disease or change in neurologic condition between the two age groups.

### Process of Care and Outcomes

Older patients were less likely to have HIV mentioned in their progress notes (69.5% vs 82.3%,  $P < .001$ ) and to receive anti-PCP medications within the first 2 days of hospitalization (85.8% vs 92.9%,  $P < .002$ ), while rates of adjunctive corticosteroids use within 3 days thereafter were higher (58.4% vs 50.1%,  $P < .054$ ). Older patients were more likely to receive care in an ICU (22.0% vs 12.8%,  $P < .002$ ) and be intubated (14.6% vs 8.4%,  $P < .012$ ). They also had 20% longer lengths of stay (mean, 12.4 days vs 10.3 days,  $P < .027$ ). Patients >50 years of age were 1.8 times more likely to die in the hospital than younger patients (18.3% vs 10.4%,  $P < .003$ ).

### Multivariate Analysis

The unadjusted odds ratio [OR] for in-hospital mortality for patients ≥50 years of age, in comparison to younger patients, was 1.8 (95% confidence interval [CI], 1.1 to 2.9 [Table 2]). When severity scores of PCP illness, use of PCP medications within 2 days of admission, and use of steroids within 3 days of starting PCP medications were added to the model, older age was no longer a significant predictor of mortality (OR, 1.3; 95% CI, 0.74 to 2.1). Severity of illness was the most significant predictor of mortality in additional logistic regression models, which included adjustments for severity of illness and process of care variables such as prior PCP prophylaxis, ICU utilization, and intubation (data not shown).

### DISCUSSION

In this study of 1,861 patients hospitalized with HIV-related PCP between the years 1995 and 1997, we found: 1) age-related differences in PCP severity of illness and an almost 2-fold higher inpatient mortality rate among older patients, and 2) while the overall timeliness of PCP medication initiation improved from 75% in the late 1980s to 90% during the years 1995 to 1997, patients ≥50 years of age continued to be less likely than younger patients to receive timely anti-PCP medications (Table 1). However, logistic regression analyses with in-hospital mortality as the outcome revealed that older age was no longer a significant predictor of inpatient mortality, after adjusting for severity of illness, timely PCP medication, and timely steroid use (Table 2).

Taken together, the results of our studies on age and PCP from the 1980s and 1990s consistently identify age-related gaps in important elements of the process of PCP care<sup>7</sup> (Table 3). Rates of recording HIV infection in the progress notes were 10% lower for older versus younger HIV-infected PCP patients during both time periods, 1987–1990 and 1995–1997, suggesting that recognition

**Table 2. Logistic Regression Models of Mortality**

	Adjusted Odds Ratio (95% Confidence Interval)		
	Model 1*	Model 2*	Model 3*
Age <50	1.0	1.0	1.0
Age ≥50	1.8 (1.1 to 2.9)	1.3 (0.8 to 2.2)	1.3 (0.7 to 2.1)
Severity score <sup>8</sup>			
Stage 1		1.0	1.0
Stage 2		2.7 (1.5 to 4.8)	2.7 (1.5 to 4.9)
Stage 3		5.1 (3.2 to 8.2)	4.8 (3.0 to 7.8)
Stage 4		8.2 (4.3 to 15.7)	7.9 (4.1 to 15.3)
Stage 5		23.7 (13.0 to 43.4)	22.0 (11.8 to 40.9)
Timely PCP medication			
No			1.0
Yes			0.6 (0.3 to 1.1)
Timely steroid use			
No			1.0
Yes			1.3 (0.8 to 2.0)

\* Mortality model 1 is based on age alone; model 2 on age and severity; and model 3 on age, severity, timely PCP medication, and timely steroid use.

Note: The goodness-of-fit measure for the logistic regression models (termed the Akaike Information Criterion [AIC]) indicated that severity adjustment (model 2) returned a 125% improvement in model performance compared to model 1 and that adding process of care measures (model 3) resulted in an additional 1% improvement in model performance.

of HIV infection was less frequent among older individuals. Older patients were more likely to present with greater severity of PCP than younger patients in both time periods, raising concern over the possibility of delayed recognition of pneumonia in older patients. Alternatively, biologic reasons may account for some of the age-related differences in severity of illness at presentation.<sup>16-18</sup> Also, while rates of timely anti-PCP medication use increased by 20% for older and 16% for younger patients with HIV-related

PCP between the late 1980s and mid-1990s, older patients were 50% to 60% as likely to have received timely anti-PCP medications. These results suggest that during both the late 1980s and the mid-1990s, physicians may have overlooked the diagnosis of PCP more often when evaluating older patients. For all patients hospitalized with HIV-related PCP in both time periods, patients ≥50 years of age were almost twice as likely as younger patients to receive care in an intensive care unit and to die in-hospital.<sup>19,20</sup> Our logistic regression models suggest that the age-related difference in in-hospital mortality may be due to variations in recognition of HIV infection, pneumonia, and/or PCP as the likely etiologic agent.

Following publication of our finding of age-related variations in practice during the 1980s, Justice and Whalen presented physicians with a number of diagnostic and therapeutic challenges regarding age-related differences in care for individuals infected with HIV and associated opportunistic infections.<sup>21</sup> These included recommendations to develop strategies that would increase awareness of the possibility of HIV infection in older individuals, identify how HIV management recommendations should be altered for older individuals, and conduct comparative studies of immune function of HIV-infected older versus younger individuals and with uninfected older individuals. This current study's results suggest that, while some progress has been made, additional efforts are needed to address these recommendations.

We recognize the need for caution in interpreting our findings. The data was abstracted from medical records. There may have been incompleteness in data recording. However, as in our earlier study, we employed reliable methods for ensuring the completeness and accuracy of data collection efforts and focused on clinical and laboratory information that is generally included in the overwhelming majority of medical records in HIV-related PCP cases. Another limitation is that our findings are from a period just prior to widespread use of HAART, with only 9% of our study patients having received protease inhibitors. Delays in conducting the study due to Institutional Review Board considerations at the 78 study hospitals was the main factor accounting for the extended study duration.<sup>22</sup> Since early 1997, the rates of opportunistic infections such

**Table 3. Conceptual Association of Age-related Variations in Patterns of Care with Medical Record Findings**

Process of Care Element	Medical Record Finding	1987-1990*		1995-1997*	
		Age <50, %	Age ≥50, %	Age <50, %	Age ≥50, %
HIV recognition	Recording of HIV in the progress notes	85	75	82	70
Pneumonia recognition prior to admission	A-a O <sub>2</sub> gradient >48.5 mm Hg <sup>†</sup>	39	54	43	57
PCP recognition	Timely initiation of PCP medications	77	66	93	86

\* Age-related differences in rates of reporting of HIV in the progress notes, A-a O<sub>2</sub> gradient, and rates of timely initiation of PCP medications were statistically significant (P < .05) during both time periods.

<sup>†</sup> In order to compare severity of illness (SOI) between different SOI staging systems used in the 2 time periods, an A-a O<sub>2</sub> gradient >48.5 mm Hg was chosen to serve as a proxy for greater severity of PCP illness, as outlined in Ref. 8.

as PCP have declined dramatically, primarily as a result of protease inhibitor therapy.<sup>23</sup> It is likely that even with these changes, delays in initiation of anti-PCP medications or corticosteroids will continue as physicians pursue other possible infectious causes of pulmonary findings in older individuals with pneumonia, many of whom are likely to have both unrecognized HIV-infection and unsuspected PCP infection. A third limitation is the absence of confirmed diagnoses of PCP in about one third of the patients in the study. While clinicians continue to debate the necessity of diagnostic bronchoscopy versus empiric PCP treatment for HIV-infected individuals who present with symptoms characteristic of PCP, rates of empiric treatment of PCP were almost 60% in both the 1980s and in the 1990s.<sup>7</sup> Also, in both time periods, the results of the multivariate analyses were similar when the study sample was limited to confirmed PCP cases. Fourth, evaluations of variations in outpatient HIV care was not the primary aim of this study. Nonetheless, the finding of lower rates of HIV-recognition, PCP prophylaxis, and antiretroviral therapy among older versus younger patients in this study raises concern that age-related variations in many aspects of HIV care may exist.

In summary, the conclusions from the present study of HIV-related PCP care and outcomes in the mid-1990s are consistent with those of our earlier PCP study from the late 1980s.<sup>7</sup>

During the 2 decades of AIDS in the United States, physicians have consistently perceived AIDS as a younger persons' disease. Even in the mid-1990s, older patients with HIV-related PCP continued to have higher rates of absent notation about HIV-risk factors in the medical record, severe PCP cases at admission, intensive care unit use during the hospitalization, and in-hospital mortality, while having lower rates of use of timely anti-PCP medications. The presence of a sizeable number of older individuals with HIV infection in the third decade of the AIDS epidemic will undoubtedly present the medical profession with new challenges and opportunities.

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