Survival of Patients with AIDS, after Diagnosis of *Pneumocystis carinii* Pneumonia, in the United States

Mark S. Dworkin,1,a Debra L. Hanson,1 Thomas R. Navin,2 and the Adult and Adolescent Spectrum HIV Disease Projectb

To examine survival after diagnosis of *Pneumocystis carinii* pneumonia (PCP) and factors associated with early death (during the month of or the month after diagnosis of PCP), data were analyzed from the Adult and Adolescent Spectrum HIV Disease project. Among 4412 patients with 5222 episodes of PCP during follow-up (1992–1998), survival at \>1 month after diagnosis was 82%, and survival at \>12 months after diagnosis was 47%; 12-month survival increased from 40% in 1992–1993 to 63% in 1996–1998. By multiple logistic regression analysis, early death was associated with history of PCP (odds ratio [OR], 1.4), age 45–59 years (OR, 1.9) or \>60 years (OR, 3.7), and CD4 cell count of 0–24 cells/μL (\<5 months before PCP; OR, 1.8) or 25–49 cells/μL (OR, 1.4) (P < .05). Concurrent prescription of combination antiretroviral therapy (OR, 0.2) and other antiretroviral therapy (OR, 0.4) was associated with surviving the early period. This study shows improved survival after diagnosis of PCP in recent years, despite emergence of antibiotic-resistant mutant *P. carinii* strains.

*Pneumocystis carinii* pneumonia (PCP) is the most commonly reported AIDS opportunistic infection in the United States, despite decreases in the incidence of opportunistic infections during the era of highly active antiretroviral therapy (HAART) [1]. Since AIDS was first recognized, improvements in treatment of PCP, use of the intensive care unit for patients with PCP, and the use of adjunctive steroids for selected patients have contributed to longer survival after diagnosis of PCP [2, 3]. During the 1990s, trimethoprim-sulfamethoxazole was the most commonly prescribed medication for prophylaxis of PCP and was given to most eligible patients [4]. Among persons who developed PCP, in-hospital mortality from PCP has been 15%–27% for human immunodeficiency virus (HIV)-infected patients, as high as 55% for patients admitted to the intensive care unit [5], and 80% for patients needing mechanical ventilator support [2, 6].

Despite these advances, there are concerns that antimicrobial resistance of *P. carinii* to trimethoprim-sulfamethoxazole, the drug of choice for treatment and prophylaxis [7], may be shortening survival after diagnosis of PCP. Specifically, a recent study of HIV-infected patients by Danish investigators [8] demonstrated a significantly lower rate of survival 3 months after diagnosis of PCP for patients with *P. carinii* point mutations in the dihydropteroate synthase (DHPS) gene. These mutations were significantly more common among patients who had previously taken sulfa drugs than among those who had not. Because prophylaxis with trimethoprim-sulfamethoxazole has been recommended for more than a decade for all HIV-infected patients with a CD4 cell count of \>200 cells/μL (OR, 1.4) (P < .05), this finding could be a harbinger of an important emerging antimicrobial resistance pattern. Also of concern is the recent finding that \>80% of patients with PCP in San Francisco were infected with mutant strains [9]; other data indicate that clinical outcomes for patients with PCP caused by the mutant strain are poorer than those for patients with the wild-type strain [8, 10].

If the prevalence of the mutant strains has been increasing in the United States, possibly in response to the widespread use of sulfa (or sulfone) drugs by HIV-infected patients [4], and if this increase is associated with poorer survival, then a decreasing trend in short-term survival after diagnosis of PCP would have been expected during the 1990s, especially in later years. To examine trends in survival after diagnosis of PCP, we analyzed data from a large US cohort study.

**Methods**

Data for this study were obtained from the Adult and Adolescent Spectrum of HIV Disease (ASD) project. The ASD project is a national surveillance project of the Centers for Disease Control...
and Prevention (CDC) in collaboration with 11 state and local health departments. In this study, information is abstracted from the medical records of HIV-infected patients at selected health care facilities. Of the facilities that participate, ∼70% are public, and ∼30% are private [1].

The initial data abstraction is a review of the 12 months before enrollment; data for AIDS-defining conditions are recorded, if available, for any time before enrollment. The initial abstraction is followed by abstractions every 6 months until the patient dies or is lost to follow-up. Data collection began in 1990 (Atlanta, Dallas, Houston, San Antonio, Denver, Detroit, Los Angeles, New Orleans, and Seattle), 1991 (New York City), and 1992 (Bayamon, Puerto Rico). The more than 100 participating facilities included hospitals, outpatient offices, and emergency rooms. Data in this analysis were collected through December 1999. To make the ASD project similar to national AIDS reports, sampling of patients for inclusion was done at some sites, as follows: in Atlanta, 50% of African American males since January 1994; in Dallas, San Antonio, and selected sites in Seattle, 25%–50% of white males since 1990–1991; for some sites in Los Angeles, no white males (except injection drug users) since 1992; in Detroit, 40%–50% of all males since 1993; and for some sites in New York City, 16% (since January 1995) to 50% of white males. Data are abstracted from multiple participating health care facilities, for a given patient.

All episodes of PCP presumptively or definitively diagnosed, according to the 1993 CDC AIDS surveillance case definition [11], during prospective follow-up during 1992–1998 were included in this analysis. A separate analysis for comparison was restricted to definitive diagnoses of PCP. Data from the ASD project include the date of diagnosis of PCP and the date of death but do not include duration of symptoms before treatment, oxygen status at diagnosis, and start and stop dates for most medications.

Survival rates by time since diagnosis of PCP were estimated by using the Kaplan-Meier method [12]. Survival probability curves for PCP episodes diagnosed during 1990–1992, 1993–1995, and 1996–1998 were constructed. Multiple logistic regression [13] was used to assess risk for early death after diagnosis of PCP, in association with calendar period of diagnosis. Early death was defined as death during the month of or the month after diagnosis. The regression model controlled for potential confounding risk factors for mortality due to PCP. The model covariates, assessed at diagnosis of PCP, included calendar period (1992–1993, 1994–1995, or 1996–1998), history of PCP, CD4 cell count ≤5 months before diagnosis of PCP (<25, 25–49, or ≥50 cells/μL or missing), use of antiretroviral therapy at time of diagnosis of PCP, patient age (13–24, 25–44, 45–59, or ≥60 years), and the ASD project site.

The regression model controlled for potential confounding risk factors for mortality due to PCP. The model covariates, assessed at diagnosis of PCP, included calendar period (1992–1993, 1994–1995, or 1996–1998), history of PCP, CD4 cell count ≤5 months before diagnosis of PCP (<25, 25–49, or ≥50 cells/μL or missing), use of antiretroviral therapy at time of diagnosis of PCP, patient age (13–24, 25–44, 45–59, or ≥60 years), and the ASD project site.

Results

PCP was diagnosed for 4412 patients (5222 episodes, of which 3255 [62%] were primary PCP). Of the study population, 35% were white, 45% were black, and 18% were women; mode of HIV transmission was male-male sex for 48%, and 20% were heterosexual injection drug users. The median age was 34 years.

Overall, survival beyond the month after diagnosis of PCP was 82%; 12-month survival after diagnosis of PCP was 47%.

Twelve-month survival increased from 40% (95% confidence interval [CI], 38–42) during 1992–1993 to 44% (95% CI, 42–46) during 1994–1995 and then to 63% (95% CI, 60–66) during 1996–1998 (figure 1; 12-month survival was 41% for 1992, 39% for 1993, 42% for 1994, 46% for 1995, 63% for 1996, 67% for 1997, and 68% for 1998). In the multivariate model, diagnosis during later calendar periods was associated with longer survival. Specifically, compared with 1992–1993, the odds ratio [OR] for early death was 0.7 (95% CI, 0.6–0.8) for 1994–1995 and 0.7 (95% CI, 0.5–0.9) for 1996–1998. Repeating the analysis only for definitive diagnoses of PCP revealed similar results (data not shown). Examination of a variable for time-dependent use of PCP treatment/prophylaxis was not found to be a confounder for calendar period.

Factors associated with significant increased risk for early death (P < .05) were history of PCP (OR, 1.4), age 45–59 years (OR, 1.9) or ≥60 years (OR, 3.7) (referent, 25–44 years), and CD4 cell count (within 6 months of PCP diagnosis) of 0–24 cells/μL (OR, 1.8) or 25–49 CD4 cells/μL (OR, 1.4) (referent, ≥50 cells/μL). Factors associated with surviving this early period were prescription of combination antiretroviral therapy (≥2 antiretroviral drugs, excluding regimens discouraged in published guidelines [14]; OR, 0.2) and prescription of other antiretroviral therapy (OR, 0.4) (referent, no antiretroviral therapy). Risk factors associated with survival prognosis did not differ for primary versus secondary episodes of PCP.

Discussion

We found that, among HIV-infected patients, short-term and 12-month survival after diagnosis of PCP increased during the 1990s, especially after the introduction of HAART in late 1995. Factors associated with poor short-term survival were history of PCP, older age, and very low CD4 cell count. Our finding of 18% mortality within 1 month of diagnosis of PCP is con-
sistent with previously reported hospital mortality rates [5]. Together with the increased risk of poor survival associated with history of PCP, our data emphasize the need to improve access to PCP prophylaxis, especially for persons who may be more likely to develop PCP and experience early death.

Our findings suggest that the mutant strains of P. carinii either did not cause many of the cases of PCP in our study population (derived from 11 US cities with moderate-to-severe HIV epidemics) or that the mutant strain, despite increasing prevalence, is not significantly affecting survival after diagnosis of PCP. Our study had several important differences from the recent study by Danish investigators [8] in which the survival rate was significantly lower 3 months after diagnosis of PCP for patients infected with mutant P. carinii strains. Our study did not include DNA analysis of P. carinii strains; therefore, a direct determination of the effect on survival by wild-type and mutant strains cannot be presented here. Also, in the study by Helweg-Larsen et al. [8], the rate of P. carinii DHPS mutations increased during 1989–1996 and then decreased during 1997–1999. The decrease was explained as having been due to an increase in the proportion of patients for whom PCP was the first symptom of HIV infection, which caused an increase in the proportion of patients with PCP who had taken little, if any, sulfa. A similar trend in PCP cases was reported in the United States [4], although without information on DHPS mutations. In the United States, a decrease in infections caused by the mutant strain during 1996–1998 could explain our finding of longer survival in recent years, without compromising the theory that DHPS mutations adversely affect survival.

In another recent study [10], among 97 patients with AIDS in 4 US cities (including Detroit and Denver, which participate in the ASD project), duration of sulfa or sulfone prophylaxis increased the likelihood of a DHPS mutation (although not to a large degree). These findings indicate that the incidence of DHPS mutations may differ considerably by geographic location. However, there was no significant association between dose of sulfa or sulfone agent and risk for a DHPS mutation or shorter survival at the completion of therapy among patients who had a DHPS mutation versus those who did not. The results of our study are consistent with the finding of no survival disadvantage for US patients with the DHPS mutations.

Finally, another recent multicenter US study showed improved survival of patients with AIDS who had PCP-induced acute respiratory failure during 1995–1999, compared with 1992–1995 [15]. Although results in the study by Curtis et al. [15] and the results of our study reflect that, in recent years, survival after diagnosis of PCP is longer in the United States (63% of patients in the study by Curtis et al. initially were treated with trimethoprim-sulfamethoxazole); however, prior use of PCP prophylaxis (which may have included nonsulfa or sulfone drugs) was associated with decreased survival.

A limitation of our study is that the ASD project is not population based and thus may not be generalizable to the HIV-infected population. However, this study is very large (>50,000 patients) and diverse (>100 inpatient and outpatient facilities), and most ASD project hospitals and clinics were selected for study participation because they reported a large percentage of the HIV and AIDS cases in their cities. Also, because our study does not include information on DHPS mutations, we cannot directly correlate their potential influence with our findings. Although a potential limitation of our study is how well mortality data were obtained, the ASD project follows patients until death or loss to follow-up at participating facilities, and most sites match to AIDS case reports and perform active surveillance for deaths by reviewing death certificates, thus giving this study a high level of completeness for reporting of mortality data.

In conclusion, we found longer survival after diagnosis of PCP in recent years, despite reports of the emergence of mutant antibiotic-resistant P. carinii strains. We did not find an increase in recent years in short-term mortality rates among HIV-infected patients with PCP, as would be predicted if the DHPS mutation in P. carinii (which has increased in prevalence) causes decreased short-term survival. Even in the Danish study [8], DHPS mutations were not associated with failure of sulfa-drug therapy; standard treatment with cotrimoxazole was successful in 12 of 19 PCP episodes caused by mutant strains. However, because exposure to sulfa drugs has been correlated with the presence of the mutant genotype and since our study found that a history of PCP (often treated with sulfa drugs) was associated with early death, the theory that the DHPS mutant affects survival has not been disproved. It is important that studies such as the ASD project continue to monitor trends in survival after diagnosis of PCP while researchers study the prevalence of antibiotic-resistant mutations and the effect of those mutations on short-term survival.

**Adult and Adolescent Spectrum of HIV Disease Project**

Project members and locations are as follows: Melanie Thompson and Julia Gable (AIDS Research Consortium of Atlanta); Sylvia Odem and Sharon Melville (Texas Department of Health, Austin); Arthur Davidson, David L. Cohn, and Cornelius Rietmeijer (Denver Department of Health and Hospitals); Linda L. Worthing and Eve D. Mokotoff (Michigan Department of Community Health, Detroit); Wes McNeely and Kaye Reynolds (Houston Department of Health and Human Services); Jane Turner and Dorothy Masters (Los Angeles County Department of Health Services); Anne Morse and Stephanie Broyles (Louisiana Office of Public Health, New Orleans); Judy Sackoff (City of New York Department of Health); Jose Otero, Robert Hunter, and Maria de los Angeles Gomez (University Central del Caribe, Bayamon, Puerto Rico); Sandra Miranda (Puerto Rico Department of Health, San Juan); and Susan Buskin, Sharon G. Hopkins, and Beth Sohlberg (Seattle–King County Department of Public Health).
Acknowledgments

We thank Pei-Chun T. Wan and Michael R. Adams for assistance with data management, A. D. McNaghten for assistance with Adult and Adolescent Spectrum of HIV Disease project management, and Patricia Fleming for manuscript review.

References