Impact of Protease Inhibitors and Other Antiretroviral Treatments on Acquired Immunodeficiency Syndrome Survival in San Francisco, California, 1987–1996

Sandra K. Schwarcz,1 Ling Chin Hsu,1 Eric Vittinghoff,1,2 and Mitchell H. Katz1

The authors assessed temporal trends in acquired immunodeficiency syndrome (AIDS) survival for 15,271 persons in San Francisco, California, diagnosed between 1987 and 1996 with an opportunistic illness included in the 1987 AIDS case definition. Predictors of survival were evaluated for 5,686 persons who were diagnosed between 1993 and 1996 and met the 1993 AIDS case definition. Median survival was 19 months for persons diagnosed between 1987 and 1989, 17 months for persons diagnosed between 1990 and 1992, 15 months for persons diagnosed between 1993 and 1994, and 31 months for persons diagnosed between 1995 and 1996. Decreased mortality was associated with use of antiretroviral therapy without protease inhibitors before AIDS (relative hazard (RH) = 0.88, 95% confidence interval (CI): 0.8, 1.0) and after AIDS (RH = 0.83, 95% CI: 0.7, 0.9) and use of antiretroviral agents with protease inhibitors before AIDS (RH = 0.25, 95% CI: 0.2, 0.3) and after AIDS (RH = 0.36, 95% CI: 0.3, 0.4). Increased mortality was found for persons aged ≥40 years (RH = 1.43, 95% CI: 1.3, 1.6), persons initially diagnosed with an opportunistic illness (RH = 1.97, 95% CI: 1.8, 2.2), and homosexual injection drug users (RH = 1.33, 95% CI: 1.2, 1.5). Survival after AIDS has increased. Treatment with antiretroviral agents, particularly protease inhibitors, strongly predicts improved survival.


acquired immunodeficiency syndrome; HIV; HIV protease inhibitors; protease inhibitors; survival

Several recent clinical trials (1–3), a cohort study (4), and clinic-based studies (5, 6) have shown that combination antiretroviral regimens with protease inhibitors decrease the morbidity and mortality associated with human immunodeficiency virus (HIV) infection. However, the effectiveness of these agents in the general population has not been demonstrated.

Protease inhibitors may not be as effective in the general population as they have been in participants enrolled in clinical trials. Regimens that include protease inhibitors can be difficult to adhere to because of the large number of pills required, frequent dosing, side effects, and drug interactions (7, 8). Substance users, homeless persons, and the mentally ill are likely to have greater difficulty complying with HIV treatments (9) and are likely to be underrepresented in clinical trials. The Multicenter AIDS Cohort Study, which found increased time to acquired immunodeficiency syndrome (AIDS) and to death among HIV-infected persons seen during the calendar years in which protease inhibitors were available, included only gay and bisexual men, thus limiting the ability to generalize the results (4). The two clinic-based studies were performed in specialized HIV treatment centers (5, 6); survival is known to be longer for HIV-infected persons cared for by HIV-experienced physicians (10). Therefore, we undertook a population-based study of the impact of antiretroviral medications on AIDS survival among persons reported with AIDS in San Francisco, California, and compared the effectiveness of treatments among demographic and risk subgroups.

MATERIALS AND METHODS

Study population

We included persons diagnosed with AIDS in San Francisco (aged ≥13 years) between January 1, 1987, and December 31, 1996, and reported to the Department of Public Health through July 31, 1998. AIDS cases were reported primarily (72 percent) through active surveillance conducted at facilities with the largest numbers of AIDS cases. The remainder of cases was reported through passive surveillance (16 percent), review of local death certificates (4 percent), and retrospective reviews and reports from other health departments (8 percent). In a 1996 evaluation, AIDS case reporting was found to be 97 percent complete (11). This percentage is consistent with previous evaluations of AIDS surveillance in San Francisco that have found reporting to be highly complete (12, 13). Residents of San Francisco who were diagnosed with AIDS outside of San Francisco Department of Public Health, San Francisco, CA. 2 Department of Epidemiology and Biostatistics, University of California, San Francisco, CA.

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Abbreviations: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; RH, relative hazard.

San Francisco Department of Public Health, San Francisco, CA.

Department of Epidemiology and Biostatistics, University of California, San Francisco, CA.

Reprint requests to Dr. Sandra K. Schwarcz, San Francisco Department of Public Health, 25 Van Ness Avenue, Suite 500, San Francisco, CA 94102 (e-mail: Sandy_Schwarcz@dph.sf.ca.us).
Francisco were excluded from the sample because of incomplete data. Information on subsequent AIDS-indicator opportunistic illnesses, interval CD4 test results, and use and starting dates of antiretroviral and prophylactic medications was obtained through prospective and retrospective reviews of laboratory records and medical charts.

Dates of death were obtained through weekly review of local death certificates and annual matches with the National Death Index. The most recent match with the National Death Index included deaths that occurred through December 31, 1996.

Analysis of survival trends

Survival was calculated as the time between AIDS diagnosis and death. Consistent with other studies of survival after AIDS, we included all-cause mortality (14–21). Persons diagnosed with AIDS at autopsy were excluded because their date of AIDS diagnosis could not be determined. Because survival has been shown to be longer for persons meeting the 1993 AIDS case definition than for persons meeting earlier case definitions (22, 23), we used the date of the first AIDS-defining opportunistic illness as the date of AIDS diagnosis and excluded persons who met only the 1993 AIDS case definition. Persons not known to have died were censored at the date of their last known follow-up or at December 31, 1996, whichever was more recent. We used the Kaplan-Meier product limit method to calculate the median number of months of survival after AIDS and the proportion of persons surviving 1 and 2 years after diagnosis. To evaluate temporal trends in survival, we examined survival for persons diagnosed with AIDS in four temporal cohorts: 1987–1989, 1990–1992, 1993–1994, and 1995–1996. These time periods were selected to distinguish the years during which zidovudine (1987–1989), didanosine and zalcitabine (1990–1992), and protease inhibitors (1995–1996) became widely available.

Analysis of impact of treatment on AIDS survival

To examine the impact of protease inhibitors and other antiretroviral treatments on AIDS survival, we limited our analysis to persons diagnosed between January 1, 1993, and December 31, 1996. Since the same 1993 AIDS case definition was in place during this time, we were able to include in this analysis persons who met either the 1993 or the earlier AIDS case definitions (24, 25). Survival was calculated from the time that a person first met the 1993 case definition to death. We calculated the predictors of survival by using the Cox proportional hazards model.

Antiretroviral treatment was classified into one of five categories: 1) no antiretroviral treatment; 2) antiretroviral therapy initiated prior to AIDS, without a protease inhibitor; 3) antiretroviral therapy initiated prior to AIDS and a protease inhibitor initiated after AIDS; 4) antiretroviral therapy initiated after AIDS, without a protease inhibitor; and 5) antiretroviral therapy initiated after AIDS, with a protease inhibitor. Because only a few persons began treatment with protease inhibitors prior to receiving an AIDS diagnosis (n = 55), we did not include a separate treatment category for antiretroviral therapy with a protease inhibitor initiated prior to AIDS. For these persons, the date of AIDS diagnosis was used as the starting date of treatment with protease inhibitors.

Because subjects could be classified sequentially into as many as three treatment categories (e.g., no treatment, then treatment with an antiretroviral initiated after AIDS, then treatment with an antiretroviral plus a protease inhibitor), we characterized treatment use in the study population by summing person-time spent in each treatment category. In the Cox models for survival, this classification was implemented by using time-dependent variables so that subjects could be reclassified if they initiated antiretroviral therapy and then protease inhibitors after AIDS was diagnosed. We avoided use of fixed covariates to represent treatment history since it may induce selection bias regarding treatment of survivors, as persons who survive longer have a greater chance of receiving treatment (26). Because information on treatment adherence and withdrawal was incomplete, we did not reclassify subjects if treatment was discontinued. To evaluate the proportional hazards model assumption, we assessed potential interactions between the time since AIDS diagnosis and each treatment category.

In our multivariable model, we also included other potential predictors of survival. These factors were age, gender, race/ethnicity, risk group, CD4 count within 3 months of AIDS diagnosis, the AIDS-defining diagnosis (the presence or absence of an AIDS-defining opportunistic illness), and use of primary prophylaxis against Pneumocystis carinii pneumonia or Mycobacterium avium complex.

In three supplementary models, we compared the effectiveness of various treatments between men and women; between Whites, African Americans, and Latinos; and between homosexual men, homosexual men who also inject drugs, and heterosexual injection drug users. In each of these three models, separate time-dependent indicators specific to the various demographic or risk groups were evaluated for the treatment categories already described. The Wald chi-square test was used to assess differences in treatment effects by demographic and risk category. All statistical tests were conducted by using SAS software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Trends in AIDS survival

A total of 20,362 persons (aged ≥13 years) were diagnosed with AIDS in San Francisco between 1987 and 1996. Of these, 15,271 (75 percent) had developed, before December 31, 1996, at least one of the opportunistic illnesses included in the 1987 AIDS case definition (24). Eighty-six percent of this sample had died. We excluded eight persons for whom the month of opportunistic illness diagnosis was unknown.

Median survival was 19 months for persons diagnosed between 1987 and 1989, 17 months for persons diagnosed between 1990 and 1992, 15 months for persons diagnosed between 1993 and 1994, and 31 months for persons diag-
nosed between 1995 and 1996 (figure 1). The cumulative proportion of persons who survived 1 and 2 years, respectively, after diagnosis was 64 and 37 percent for persons diagnosed between 1987 and 1989, 62 and 35 percent for persons diagnosed between 1990 and 1992, 57 and 34 percent for persons diagnosed between 1993 and 1994, and 63 and 53 percent for persons diagnosed between 1995 and 1996.

Impact of treatment on AIDS survival

A total of 6,997 persons were diagnosed with AIDS between January 1, 1993, and December 31, 1996. Of these, 1,311 (19 percent) were excluded from the Cox proportional hazards model because of missing treatment or CD4 test result information. The demographic characteristics of persons excluded from analysis were similar to those who were included (data not shown). Of the 5,686 persons included in the Cox proportional hazards analysis, 32 percent were known to have died.

In the multivariate analysis, the hazard of death after AIDS was significantly greater for persons more than 40 years of age, for homosexual injection drug users, and for persons initially diagnosed with an opportunistic illness (table 1). Survival was somewhat worse for men and heterosexual injection drug users than for women or noninjection drug users. Risk of death after AIDS was similar among the race and ethnic groups evaluated. A higher CD4 cell count at the time of AIDS diagnosis predicted longer survival.

Receipt of antiretroviral agents without a protease inhibitor before or after AIDS significantly reduced the risk of death. When protease inhibitors were added to other antiretroviral agents that were initiated prior to AIDS, the risk of death was lowered by 75 percent; when protease inhibitors were added to antiretroviral agents started after AIDS, the risk of death was lowered by 64 percent.

Primary prophylaxis against P. carinii pneumonia and M. avium complex was not associated with improved survival. To evaluate the effect of secondary P. carinii pneumonia prophylaxis on survival, we restricted the analysis to the 1,131 persons with P. carinii pneumonia. Secondary P. carinii pneumonia prophylaxis did not improve survival (relative hazard (RH) = 1.02, 95 percent confidence interval (CI): 0.8, 1.3).

Results of the univariate analysis of the predictors of mortality were consistent with those of the multivariate analysis, except that the unadjusted risk of death was significantly greater for African Americans (RH = 1.3, 95 percent CI: 1.1, 1.5) and the unadjusted risk of death was lower with primary P. carinii pneumonia prophylaxis (RH = 0.76, 95 percent CI: 0.7, 0.8). We found that the risk ratios for the interaction terms between each of the treatment categories and survival time exceeded 1.00 (RH range = 1.03–1.05, p < 0.001 for each treatment category), indicating that although the protective effect persisted, it was attenuated slightly over time.

Antiretroviral regimens with protease inhibitors, when used prior to or after AIDS, were effective for all subgroups evaluated (table 2). Treatment after AIDS was more effective for Whites (RH = 0.25, 95 percent CI: 0.2, 0.4) than for African Americans (RH = 0.33, 95 percent CI: 0.1, 0.8; p = 0.59). The effectiveness of treatment did not differ significantly for persons in any other treatment category or between other subgroups.

DISCUSSION

Our analysis demonstrates a substantial increase in survival for persons diagnosed with AIDS between 1995 and 1996. This period coincides with the time that effective combination antiretroviral therapies were widely available (1994–1995) (27, 28) and protease inhibitors were introduced (1995–1996) (29–32). The temporal association of improved survival and expanded treatment options is substantiated further by our multivariable model showing that use of protease inhibitors was associated with a dramatic decrease in the odds of mortality. Our analysis of the effect of treatment in each demographic group indicated that protease inhibitors were effective in all subgroups that we assessed. Our results extend the findings from clinic and cohort studies (4–6) of the effectiveness of protease inhibitors for the general population.

Our study establishes that protease therapy is effective across demographic and HIV risk factor subgroups. This finding highlights the importance of addressing disparities...
in access to therapy for HIV-infected persons. For example, studies have shown that injection drug users are less likely to receive antiretroviral agents (33, 34). Although we found that protease inhibitors were as effective in injection drug users as in noninjection drug users, clinicians may have been less likely to initiate treatment for injection drug users they thought were less likely to comply with treatment. Therefore, our results do not prove that treating all injection drug users will produce levels of treatment efficacy similar to those seen for noninjection drug users. Nonetheless, our results demonstrate the importance of not excluding persons from treatment on the basis of their demographic or HIV risk group.

We found that the relative hazard of death for African Americans who received protease inhibitors with other antiretroviral agents after AIDS was higher than it was for Whites and Latinos. Since the effectiveness of protease treatment was similar for African Americans and Whites when this treatment was combined with other antiretroviral agents initiated prior to AIDS, it is unclear whether we uncovered a true disparity in effectiveness. Future studies, with larger sample sizes of African Americans and more complete treatment information, should compare treatment efficacy across ethnic groups.

Persons treated with antiretroviral agents without protease inhibitors derived benefit from these regimens, but the size of the effect was dwarfed when compared with the effect of protease inhibitors. Our finding of survival benefit with antiretroviral use is consistent with many other studies (14, 35, 36). Although some studies have found little or no survival benefit with early zidovudine treatment (14, 37, 38), our finding of improved survival with use of antiretroviral therapy before AIDS may reflect the clinical benefit associated with the additional use of didanosine (39), zalcitabine (40), and lamivudine and stavudine (41, 42) and with increased use of double- and triple-combination antiretroviral therapy. Although all treatment categories were protective, the effect of treatment was attenuated slightly over time. This finding may indicate that the duration of maximum treatment benefit is limited or that persons who received treatment for longer periods of time may have been on less-effective therapy, or it may reflect treatment failure or discontinuation for some persons.

We did not find a survival benefit associated with use of prophylaxis against *P. carinii* pneumonia or *M. avium* complex. Prior observational studies of the effect of *P. carinii* pneumonia prophylaxis on AIDS survival have produced mixed results (14, 17, 43–46). It is possible that while prophylaxis against *P. carinii* pneumonia and *M. avium* complex prevents these infections, it does not improve survival measurably after taking into account the effect of antiretroviral treatment. Alternatively, clinicians may be more likely to initiate prophylaxis for patients at higher clinical risk for *P. carinii* pneumonia or *M. avium* complex, such as those with constitutional symptoms, factors that we were unable to adjust for in this analysis. Thus, this lack of survival benefit may reflect greater use of prophylaxis by sicker patients. Since the effectiveness of treatment was similar for African Americans and Whites who received protease inhibitors with other antiretroviral agents after AIDS; treatment after AIDS analyzed as a time-dependent variable.

**TABLE 2.** Stratified proportional hazards models* of the risk of death associated with antiretroviral treatments for demographic subgroups of persons with AIDS, San Francisco, California, 1993–1996

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment category† (RH‡ (95% CI‡))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ART† before AIDS, no PI§</td>
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<tr>
<td></td>
<td>ART before AIDS + PI after AIDS¶</td>
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<tr>
<td></td>
<td>ART after AIDS, no PI#</td>
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<tr>
<td></td>
<td>ART + PI after AIDS**</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.88 (0.8, 1.0)</td>
</tr>
<tr>
<td>Female</td>
<td>0.79 (0.5, 1.3)</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
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<tr>
<td>White</td>
<td>0.87 (0.7, 1.0)</td>
</tr>
<tr>
<td>African American</td>
<td>0.85 (0.6, 1.2)</td>
</tr>
<tr>
<td>Latino</td>
<td>1.07 (0.8, 1.5)</td>
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<tr>
<td>Model 3</td>
<td></td>
</tr>
<tr>
<td>Homosexual male</td>
<td>0.84 (0.7, 1.0)</td>
</tr>
<tr>
<td>Homosexual male injection drug user</td>
<td>1.03 (0.8, 1.4)</td>
</tr>
<tr>
<td>Heterosexual injection drug user</td>
<td>0.98 (0.7, 1.4)</td>
</tr>
<tr>
<td></td>
<td>0.27 (0.1, 1.1)</td>
</tr>
</tbody>
</table>

* Each model was adjusted for all other demographic and risk variables, the CD4 count at diagnosis, and the acquired immunodeficiency syndrome (AIDS)-defining diagnosis.
† Persons in each treatment category were compared with those not receiving treatment.
‡ RH, relative hazard; CI, confidence interval; ART, antiretroviral therapy; PI, protease inhibitor.
§ Use of any antiretroviral agents other than protease inhibitors prior to onset of AIDS.
¶ Use of any antiretroviral agents other than protease inhibitors prior to onset of AIDS and use of antiretroviral agents with a protease inhibitor after AIDS; treatment after AIDS analyzed as a time-dependent variable.
# Use of any antiretroviral agents other than protease inhibitors after development of AIDS; analyzed as a time-dependent variable.
** Use of any antiretroviral agents that included a protease inhibitor after AIDS; analyzed as a time-dependent variable.
†† P = 0.06 using the Wald test comparing the effectiveness of treatment between Whites and African Americans; all other comparisons between subgroups were not statistically significant.
vival for persons diagnosed in 1990-1992 and 1993-1994 may have been due to use of *P. carinii* pneumonia prophylaxis which, by increasing the time between HIV infection and development of *P. carinii* pneumonia, resulted in persons being diagnosed with AIDS at a later stage of HIV infection (60–62). This occurrence would result in decreased time between AIDS diagnosis and death. In our study, the decline in the proportion of persons whose initial AIDS opportunistic illness was *P. carinii* pneumonia after 1990 supports this theory; 48 percent of AIDS cases diagnosed in San Francisco between 1987 and 1989 presented with *P. carinii* pneumonia compared with 34 percent of persons diagnosed between 1990 and 1994 and 26 percent of persons diagnosed between 1995 and 1996.

Our finding of worse survival among older persons has been demonstrated in virtually all studies of AIDS survival (14, 18–21, 47, 63). Survival among women was somewhat better than among men. Several earlier studies found that survival for women was worse than for men (18–20, 63), but more recent studies have found that it is similar (44, 49, 53, 56, 64). The slightly better survival among women during recent years may reflect better access to care and improvements in diagnosis and management of AIDS in women.

We did not find survival differences by race or ethnicity. This finding is consistent with the one from most other studies that adjust for prognostic indicators and access to treatment (44, 49, 51). We found that survival was worse for homosexual injection drug users. The difference may be due to less-effective treatment because of lower adherence to the regimen (65, 66) or to greater competing causes of mortality such as homicide and overdose among HIV-infected injection drug users (67, 68).

This study has several limitations. For example, surveillance data contained limited detail. Although we adjusted our analysis for CD4 counts, we were unable to adjust for HIV viral load or the presence of systemic symptoms that may influence survival. Because patients with more severe illness are more likely to receive treatment (69), we probably underestimated the survival benefit associated with use of antiretroviral agents and protease inhibitors. The information in the AIDS registry may have been incomplete; patients may have received care from providers outside of San Francisco or changed providers, and this information was not available to surveillance staff. Information collected for persons treated with antiretroviral agents is limited to the type of medication received and the date the patient was first known to be receiving the medication. As a result, our models may have classified persons as receiving treatment for a longer period than they actually did, resulting in underestimation of the survival benefit associated with treatment. We were unable to distinguish persons receiving combination antiretroviral therapy without a protease inhibitor from those receiving sequential monotherapy without a protease inhibitor.

Although previous studies have demonstrated that the long-term prognosis for AIDS is poor, recent advances in antiretroviral therapies, especially the use of protease inhibitors, provide for a more optimistic view of the prognosis for HIV-infected persons. Not yet known is whether the short-term increase in survival found in this study will translate into an improved long-term prognosis for persons with AIDS. Additional follow-up of persons with AIDS is necessary to determine the long-term effects of current and future treatments on HIV-related morbidity and mortality.

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