Epidemiological studies of HIV infection in woman
van Benthem, B.H.B.

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Chapter 3

Long-term survival after infection with human immunodeficiency virus type 1 (HIV-1) among homosexual men in hepatitis B vaccine trial cohorts in Amsterdam, New York City, and San Francisco, 1978-1995

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Long-Term Survival after Infection with Human Immunodeficiency Virus Type 1 (HIV-1) among Homosexual Men in Hepatitis B Vaccine Trial Cohorts in Amsterdam, New York City, and San Francisco, 1978—1995

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Information on long-term survival after infection with human immunodeficiency virus type 1 (HIV-1) is limited. Previously, we reported on progression of HIV-1 infection and survival up to 13 years after seroconversion. The median time from seroconversion to death was 12.3 years, and older age at seroconversion was associated with shorter survival time. Although we observed a significant increase in survival time after an acquired immunodeficiency syndrome (AIDS) diagnosis in more recent time periods, we did not find an increase in survival time from seroconversion in more recent years (1).

In this paper, we describe the long-term survival and annual risk of dying, up to 18 years and before the widespread use of highly effective drug therapies, among men who participated in the hepatitis B vaccine trials in Amsterdam, New York City, and San Francisco. Death was chosen as the endpoint because of a variety of changes over time that may have affected the time of AIDS diagnoses. These changes include improvements in AIDS-diagnosing practices and the addition of CD4 T-lymphocyte counts under 200 as an AIDS diagnosis in 1993 in the United States (2) that may result in earlier diagnosing and thus shorten the time from seroconversion to AIDS. Conversely, some treatment improvements, particularly prophylaxis for opportunistic infections, may...
serve to delay progression to AIDS and thus lengthen the incubation period to disease.

MATERIALS AND METHODS

The study population comprised participants in the hepatitis B vaccine trials in Amsterdam, New York City, and San Francisco. Detailed descriptions of these three studies and of the combined cohort have been reported previously (1, 3, 4).

Briefly, the Amsterdam cohort comprised 714 men who were first screened for a hepatitis B vaccine efficacy trial between 1977 and 1980. The New York City cohort comprised 326 men initially screened between 1977 and 1978. The San Francisco cohort included 336 men first screened between 1978 and 1980. Men from the three cohorts were invited to participate in follow-up studies of HIV-1 infection and AIDS beginning in 1983 and 1984 (1). The men included in this analysis were either already infected with HIV-1 at entry into the hepatitis B studies or were documented to have seroconverted during follow-up (n = 362; Amsterdam, n = 74; New York City, n = 120; San Francisco, n = 168).

Active follow-up and matches with the US National Death Index registry determined the occurrence of death in the New York and San Francisco cohorts, and copies of death certificates were obtained. The cause of death was obtained from review of death certificates. In Amsterdam, information on death was obtained through active follow-up and matching with local population registries. The cause of death was obtained from local AIDS surveillance registries, hospital records, and next-of-kin. Follow-up was through the end of 1995 and, thus, all men not known to be deceased were censored as of December 31, 1995.

The date of seroconversion was imputed for each participant as the expected month and year of seroconversion conditional on the participant’s last HIV-1-negative and first HIV-1-positive antibody tests and on estimated HIV-1 infection density curves for each cohort (1, 5).

The time from seroconversion to death was calculated using the Kaplan-Meier product-limit approach with pointwise 95 percent confidence intervals. Survival times for participants in the New York City cohort were calculated using left-truncation as of June 1984, since the men were required to be alive and AIDS free when entering the New York City natural history study. For all other men, survival times were truncated at the date of their first positive test. Hazard rates with a bandwidth of 1 year of time since seroconversion were calculated using person-time methods, incorporating left-truncation. Parametric models of survival time were used to help determine the shape of the hazard curve. The log-normal model that allowed for the hazard to decrease after an initial increase was compared with the Weibull model that does not allow for such change (6, 7). Proportional hazards modeling was used to examine the effects of covariates on survival time (8).

RESULTS

The San Francisco cohort was the youngest at the time of seroconversion, and the US cohorts included more minority men compared with the Amsterdam cohort (table 1). The percentage of deaths in the three cohorts did not significantly differ nor did the percentage of deaths attributable to AIDS or HIV-1 infection.

The median survival time from seroconversion to death was 12.1 years (95 percent confidence interval (CI): 11.4, 12.9), with 37.2 percent surviving at 15 years after seroconversion (95 percent CI: 31.4, 42.9). Median survival times were not significantly different among the three cohorts: Amsterdam, 11.7 years (95 percent CI: 9.6, 12.3); New York, 12.1 years (95 percent CI: 10.9, 13.6); San Francisco, 12.4 years (95 percent CI: 11.4, 14.4) (log-rank statistic p value = 0.47) (figure 1).

The risk of dying per year given survival to that year is presented in figure 2. The risk of dying increased at a relatively constant rate until 8 years after seroconversion. Parametric analysis of survival time indicated that the log-normal model fit the data better than the Weibull model (log-normal −2 log likelihood = 1,359.75; Weibull = 1,445.2), suggesting that the annual risk of dying leveled off in later years (figure 2). The risk of dying did not significantly differ by city (p value = 0.22).

In univariate analyses, older age at seroconversion and the most recent calendar time period (January 1992 to December 1995) were associated with an

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Characteristics</td>
<td>Mean age at seroconversion (years)</td>
<td>White (%)</td>
<td>Deceased (%)</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------------------------------</td>
<td>-----------</td>
<td>--------------</td>
</tr>
<tr>
<td>Amsterdam (n = 74)</td>
<td>33</td>
<td>100</td>
<td>55</td>
</tr>
<tr>
<td>New York City (n = 120)</td>
<td>32</td>
<td>90</td>
<td>58</td>
</tr>
<tr>
<td>San Francisco (n = 168)</td>
<td>29</td>
<td>93</td>
<td>57</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.01</td>
<td>0.02</td>
<td>0.92</td>
</tr>
</tbody>
</table>

* AIDS, acquired immunodeficiency syndrome
† Among those who died.
Long-term survival after HIV-1 infection


increased risk of death (table 2). However, in multivariate analysis, only older age at seroconversion was significantly associated with more rapid progression from seroconversion to death. When calendar year was replaced by year of seroconversion in the multivariate analysis, the relative hazard for those seroconverting in the most recent time period was elevated but not statistically significant (relative hazard for 1982–1985 vs. <1982 = 1.11; 95 percent CI: 0.81, 1.52; relative hazard for >1985 vs. <1982 = 1.57; 95 percent CI: 0.69, 3.60). No significant interactions were found between the calendar time period and age or city.

**DISCUSSION**

Analysis of data from the three hepatitis B vaccine cohorts with well-documented seroconverters and long-term follow-up continues to provide important information about survival after HIV-1 infection, especially for the right-hand tail of the distribution of survival times. In particular, these data have provided information on long-term survival prior to the widespread use of highly effective antiretroviral treatments, such as protease inhibitors.

In this study, the annual risk of dying increased at a fairly steady rate until about 8 years after seroconversion. Parametric modeling of the data suggested that the risk of dying leveled off in later years, although the sample size then was small. Studies of other cohorts have found that the log-normal model is an appropriate distribution for the incubation period from seroconversion to AIDS but with only limited data on models of seroconversion to death (6, 7, 9; 10). The potential leveling of the hazard prior to the widespread use of highly effective treatments suggests that there is a group of individuals who are relatively resistant to disease progression. Alternatively, this leveling of the hazard could reflect some treatment improvements, particularly prophylaxis for opportunistic infections.

A limited, rather than strong, treatment effect on long-term survival is most consistent with our finding that survival in the most recent calendar time period was not significantly different from that in earlier periods. These findings do not necessarily mean that some early antiretroviral drugs and use of primary prophylaxis for *Pneumocystis carinii* pneumonia have not been effective for the individual. Theoretically, beneficial treatment effects could also be counterbalanced by other factors, such as lack of access to treatment or variation in HIV virulence. Evidence for infection with strains of different virulence has not been observed in a number of cohort studies that used year of seroconversion as a surrogate measure (11–14), although this phenomenon has been suggested by a few other epidemiologic studies (15, 16). Studies of viral isolates from individuals infected in early and later years of the epidemic might provide additional insight into this question.

Finally, a remarkable decline in mortality among AIDS cases has been observed in some of the epicenters and in the United States beginning in 1996. Most likely this decline was a result of the success and more widespread use of new treatments, including protease inhibitors and triple-drug therapy approaches (17, 18). As a result, estimates of survival time among HIV-1-infected individuals in the absence of or with limited treatment will no longer be available. The long-term follow-up of the hepatitis B vaccine cohorts, as pre-

### TABLE 2. Cox proportional hazard analysis of progression from human immunodeficiency virus type 1 seroconversion to death among homosexual men in hepatitis B cohorts, Amsterdam, New York City, and San Francisco, 1978–1995

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. for each category*</th>
<th>Unadjusted relative hazard</th>
<th>Adjusted relative hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at seroconversion per 10 years</td>
<td></td>
<td>1.51 (1.18, 1.93)†</td>
<td>1.41 (1.07, 1.84)</td>
</tr>
<tr>
<td>Calendar time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>June 1987 and before</td>
<td>321</td>
<td>1.18 (0.62, 2.24)</td>
<td>1.00</td>
</tr>
<tr>
<td>July 1987 to June 1988</td>
<td>297</td>
<td>0.77 (0.36, 1.62)</td>
<td>1.09 (0.58, 2.06)</td>
</tr>
<tr>
<td>July 1988 to June 1989</td>
<td>289</td>
<td>1.42 (0.79, 2.56)</td>
<td>0.69 (0.33, 1.46)</td>
</tr>
<tr>
<td>July 1989 to December 1991</td>
<td>303</td>
<td>2.04 (1.09, 3.82)</td>
<td>1.18 (0.65, 2.16)</td>
</tr>
<tr>
<td>January 1992 to December 1995</td>
<td>249</td>
<td></td>
<td>1.50 (0.76, 2.96)</td>
</tr>
<tr>
<td>City</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amsterdam</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>New York City</td>
<td></td>
<td>0.67 (0.59, 1.28)</td>
<td>1.00</td>
</tr>
<tr>
<td>San Francisco</td>
<td></td>
<td>0.79 (0.55, 1.15)</td>
<td>0.96 (0.64, 1.44)</td>
</tr>
</tbody>
</table>

* One person can contribute to different calendar periods and, thus, the categories are not mutually exclusive.
† Numbers in parentheses, 95% confidence interval.
Long-term survival after HIV-1 infection

sent here, provides one of the most complete pictures of the natural history of HIV-1 infection that is currently available. Further follow-up and characterization of the group that appears to be relatively resistant are warranted.

ACKNOWLEDGMENTS

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REFERENCES
