

Differences in Susceptibility to AIDS Development: A Cohort Study of Danish and American Homosexual-Bisexual Men, 1981 to 1995

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Summary: We estimated the annual hazard rate for progression to AIDS as defined by the 1987 case definition in HIV-infected members of a cohort of Danish and American homosexual-bisexual men who were observed from 1981 to 1995. Furthermore, we extrapolated the hazard to 25 years based on imputed future time to AIDS. Of 201 HIV-positive subjects, 112 developed AIDS before the end of follow-up. The hazard increased rapidly during the first years following infection, attained a peak of about 15% per year at year 7, and was moderately lower during years 8 through 10. In subsequent analysis, we imputed future time to AIDS in 89 subjects who had not progressed by the end of follow-up by extrapolation from subject-specific CD4 trend lines. A CD4 count of ≤ 100 cells/ μ l was the best surrogate for clinical AIDS. Under this model, the imputed AIDS hazard stabilized at around 8% per year after 10 years. We projected that 13% (95% confidence interval [CI], 8%–19%) of the infected men may remain free from AIDS 25 years after seroconversion. Our direct data suggest that incubation times reflect a mixture of a population that is susceptible to disease progression and has short incubation periods with a group that is relatively resistant. Based on an extrapolation model, >10% of HIV-infected persons may survive for up to 25 years without developing AIDS. **Key Words:** Incubation period—HIV—AIDS—Homosexual men—Cohort study.

Current knowledge of the natural history of HIV infection is limited because of the relatively recent emergence of the virus.

Cohort studies have made it possible to determine the risk of AIDS up to the observed period of the epidemic. However, little is known about the distribution of extreme values of the incubation period, the so-called "tail" of the AIDS incubation distribution.

To extend estimates of the incubation distribution, we predicted the time to AIDS for subjects in our cohort of

homosexual men who had not progressed by the end of follow-up from subject-specific CD4 trend lines (1). To make these predictions, we exploited that CD4 lymphocyte counts tend to decrease with time from seroconversion, and that AIDS occurs with relatively high probability around the time a critically low CD4 count has been attained (2–4). We used these extrapolated times—and an assessment of their uncertainty—to estimate the likely percentage of HIV-infected homosexual men who will remain AIDS-free for up to 25 years.

MATERIAL AND METHODS

Subjects

The data consist of 259 Danish and 245 American homosexual-bisexual men. The Danish cohort was established in 1981 (5,6), and

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follow-up studies were performed in the years 1982, 1983, 1984, 1987, 1989, and 1992. Participants donated serum that was screened for HIV antibody, and except for the 1981 sample, the CD4 count of participants was determined. The American cohort was established in 1982 and consists of 160 homosexual men from Washington, D.C. and 85 homosexual men from Manhattan, New York City, NY, U.S.A. (7,8). Examinations took place every year from 1982 to 1992 based on the same approach as that followed in Denmark. In Denmark and the United States, the cohorts were updated with respect to AIDS and vital status on January 1, 1995 and on January 1, 1994, respectively.

Twenty-one Danes were HIV-positive on the first occasion and by 1995, another 48 were known to have become HIV-infected. AIDS, as defined by the 1987 definition, had developed in 37 cases by the end of the study. In the American cohort were 84 HIV-prevalent cases; another 49 seroconverted during the period from 1982 to 1994. In total, 76 developed AIDS. However, one prevalent case from New York City, who had AIDS at entry into the study contributed no follow-up information and therefore was excluded from further analysis, leaving 201 men at risk for AIDS development.

For the 97 incident HIV cases, the dates of their last negative and first positive HIV test results were available. For the 104 prevalent cases, only the dates of their first positive tests were available. In Denmark, the dates of HIV seroconversion for the prevalent cases were estimated as the midpoint between July 1, 1980 and the dates they were first determined to be HIV-positive. This gave an estimated date of seroconversion in March 1981. The American cohort consisted of people from both Washington, D.C. and New York City. Given that the HIV epidemic appeared a little later in Washington, D.C. than it had in New York City, the date of seroconversion was estimated as the midpoint between January 1, 1979 (New York City) or January 1, 1980 (Washington, D.C.) and the date these patients were first determined to be HIV-positive.

For estimation of the seroconversion dates of the incident cases, we used a method that addressed the interval censoring problem. This methodology is based on a generalized linear model with a logarithmic link function developed by Becker and Melbye (9) for the case in which the subjects are examined at equal time points and further developed by Carstensen (10) to cover a situation in which the subjects are not examined at equal time points. In short, this results in a piecewise exponential "survival function" for the time of seroconversion and the date of seroconversion is estimated as the median "survival time" in the interval in which the person is known to have seroconverted.

During these years, cooperation was close between the research teams in Denmark and the United States so that the results from the two countries would be easily comparable. Before 1987, HIV serology and CD4 measurements were evaluated in the same laboratory using similar methodology. More recently, these analyses have been standardized and are now undertaken in each country separately. However, change of methodology over time might have influenced the variability of the CD4 count. Hence, an adjustment was made in the CD4 counts as described previously (11). We assumed in the further analysis that the date of seroconversion was known and considered only the HIV-positive homosexual men and CD4 measurements taken between seroconversion and AIDS or loss to follow-up.

By way of background, each citizen in Denmark is assigned at birth a unique identification number, which permits accurate linkage of information from different registries. Information about AIDS and vital status was obtained through the national AIDS registry (registry in which is mandatory) and the Central Person Registry. The Central Person Registry keeps updated files on all residents in Denmark and documents such demographic variables as death and migration. Follow-up on the American cohort was conducted annually with interview

reports of events by subjects or their doctors. AIDS was diagnosed as clinical AIDS. Thus, a diagnosis based solely on a low CD4 count (using the 1993 definition) is not considered as determining AIDS for the purposes of our analysis. In Denmark and the United States, 4 and 3 people, respectively, died of causes not attributable to AIDS. These seven were censored at time of their death.

Statistical Methods

We used spline functions to estimate the annual AIDS hazard rate based on the data on time of AIDS diagnosis. This method has been described in detail elsewhere (12) and accounts for the late entry of some subjects into the cohort. Confidence limits were obtained using the bootstrap method. The analysis included a total of 201 subjects, 112 AIDS events, and 1351 person-years of follow-up.

In addition to empiric AIDS information, we further evaluated the long-term projections of AIDS in the cohort based on additional information from the sequential measurements of CD4⁺ counts. To predict the time of AIDS in an HIV-positive subject who had not yet developed AIDS, one could, as suggested by Phillips et al. (1), regress the CD4⁺ counts linearly on time for each person using the least-squares method. However, it is a general experience that the individual variability of the CD4 count measurement can be substantial and may be influenced by the initial clinical status. To take into account this individual variability, we used a *random effects* model (13), supposing that the CD4 count depends on some common level of CD4 lymphocytes and supposing that a linear time trend exists for each person but with a varying interpersonal random intercept and slope. The data were better described by a model on the square root scale as opposed to on the linear or logarithmic scales, so with t_{ij} the time that individual i had the j th CD4 measurement, $CD4_{ij}$, taken we fitted a model of the form

$$\sqrt{CD4_{ij}} = \theta + \alpha_i + (\phi + \beta_i) t_{ij} + \delta_{ij}$$

where θ and ϕ are the population intercept and slope, respectively; α_i, β_i are the random deviations from these population values for individual i , and δ_{ij} is an error term.

The model was fitted for those who had at least two CD4 measurements taken, which was the situation for 149 of the 201 HIV-recorded subjects. Of these, 34 subjects had two CD4 measurements recorded, 26 had three, 25 had four, and 64 had five or more. AIDS was predicted as the time when the estimated line reached a given CD4 level.

Kaplan-Meier estimates of the probability of remaining free of AIDS after 25 years from seroconversion were then made as follows. For those who developed AIDS before the end of study, the time to AIDS was taken as the observed time to AIDS, otherwise time to AIDS was taken as the time to the predicted date of AIDS. If the estimated slope was positive, the person was censored at 25 years from seroconversion. Moreover, people were censored at 25 years from seroconversion if they had a predicted date of AIDS beyond this time. If the onset of AIDS was predicted after seroconversion but before the time at which the person was last seen without AIDS, date of AIDS was estimated as 1 day after the time where the person was last seen without AIDS. To determine the variance of the Kaplan-Meier estimator, it was necessary to take into account the extra uncertainty arising from the predictions. We estimated the Kaplan-Meier variance using a simulation procedure. Details are given in the Appendix.

To evaluate the CD4 level at which HIV-infected subjects naturally develop AIDS-defining clinical disease, we used information of the

CD4 count up to 10 years from seroconversion to predict AIDS dates up to 14 years, for those not having an AIDS diagnosis within the first 10 years. Thus, we compared the observed Kaplan-Meier curve from 10 to 14 years (i.e., based on the actual AIDS cases observed within that interval) with the three curves obtained by estimating date of AIDS as the time when the estimated line reached a CD4 level of 50, 100, or 200, respectively, with the same restrictions as described in the previous paragraph.

RESULTS

Figure 1 shows the Kaplan-Meier curve based on the observed AIDS cases (solid line) compared with the Kaplan-Meier curves based on the observed AIDS cases within the first 10 years from seroconversion and adding the "cases" between 10 and 14 years where the estimated line reached CD4 levels of 50, 100, and 200, respectively. Comparisons, performing log-rank tests, of the Kaplan-Meier curve using a CD4 level of 50, 100, or 200, respectively, with the observed curve gave test statistics of 0.39, 0.06, and 1.08. Therefore, as also seen in Figure 1, the curve using a CD4 level of 100 corresponds best with the observed curve. Based on these findings, AIDS was predicted by the time at which the estimated line reached a CD4 level of 100.

The median time to AIDS was 8.6 years. Based on observed AIDS information, we observed an increasing hazard through the first years following seroconversion reaching a peak annual hazard rate at year seven of 0.145 (95% confidence interval [CI], 0.115–0.174). Hereafter, the hazard rate appeared to decline (Fig. 2A). In our subsequent analyses, which included imputed time to

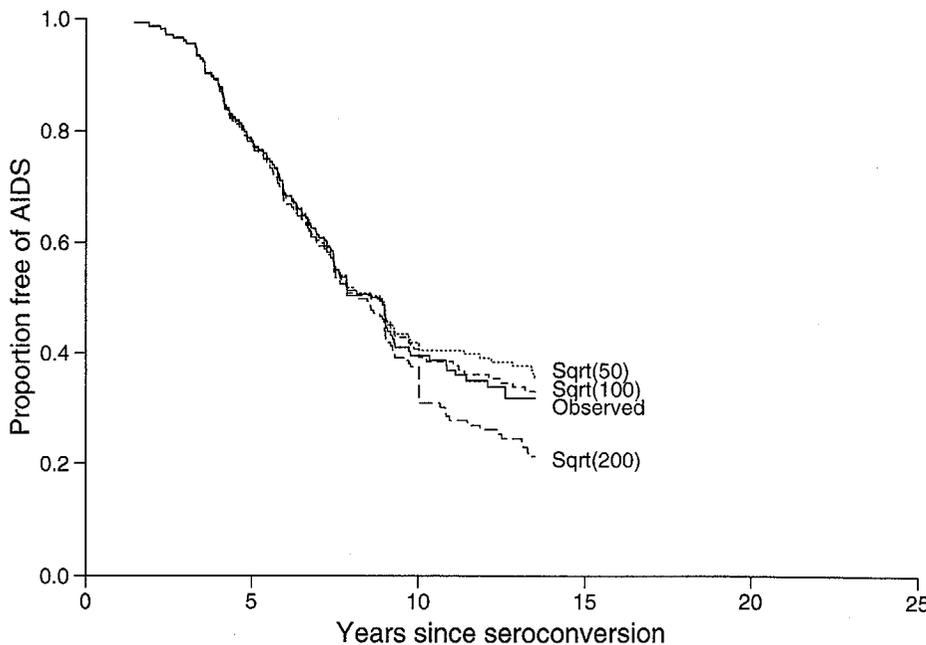


FIG. 1. AIDS-free survival based on observed AIDS cases and compared with imputed time-to-AIDS based on the observed AIDS cases within the first 10 years from seroconversion and adding cases where the estimated line reached a CD4⁺ level of 50, 100, and 200 cells/ μ l, respectively.

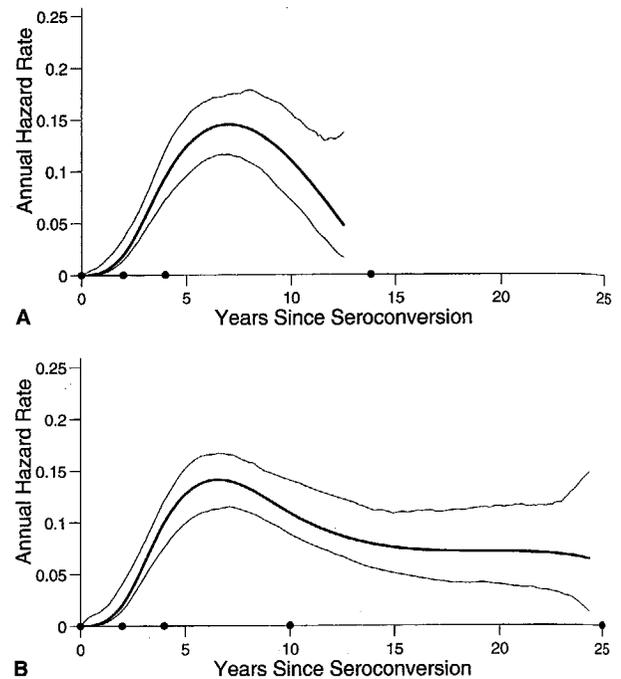


FIG. 2. Annual AIDS hazard rate in a cohort of 201 HIV-infected homosexual men. (A) Calculations based on observed AIDS diagnoses during 1981 to 1995. (B) Calculations were based on observed AIDS diagnoses during 1981 to 1995 and imputed AIDS cases (based on extrapolation of subject-specific CD4⁺ trend lines).

AIDS, we observed that the hazard rate stabilized at approximately 8% per year after 10 years since HIV infection (Fig. 2B). We subsequently estimated the hazard rates for those who seroconverted in 1982 or earlier and

for those who seroconverted in 1983 or later but found the curves to be nearly identical.

Fitting a random effects model using information from the entire follow-up period, we found using the square root scale model, that the population estimate of the $\sqrt{\text{CD4}}$ level at seroconversion was 24.12 and that for every additional year of follow-up, the average $\sqrt{\text{CD4}}$ decreased by 1.29.

In the cohorts, 112 AIDS cases were observed within the study period and we were able to predict a date of AIDS for another 61 persons. Six of these were predicted to have developed AIDS before the date they were last seen without AIDS. Eighteen people were censored at 25 years after seroconversion because the predicted time to AIDS was beyond this time.

Figure 3 shows the Kaplan-Meier estimate with thin lines corresponding to pointwise confidence limits obtained from the simulation procedure described in the Appendix. Table 1 presents the probability of remaining free of AIDS with 95% CI for every 5 years, and it is seen that an estimated mean 13% (range, 8%–19%) will be AIDS-free after 25 years.

We addressed the question whether the risk of dropping out from the study after seroconversion depended on the level of the CD4 count of the participant, for example, whether our censorship was informative or not. Based on a regression analysis and using the last measured CD4 count, we found the same effect of CD4 count over time and thus no indication that the drop-out was informative.

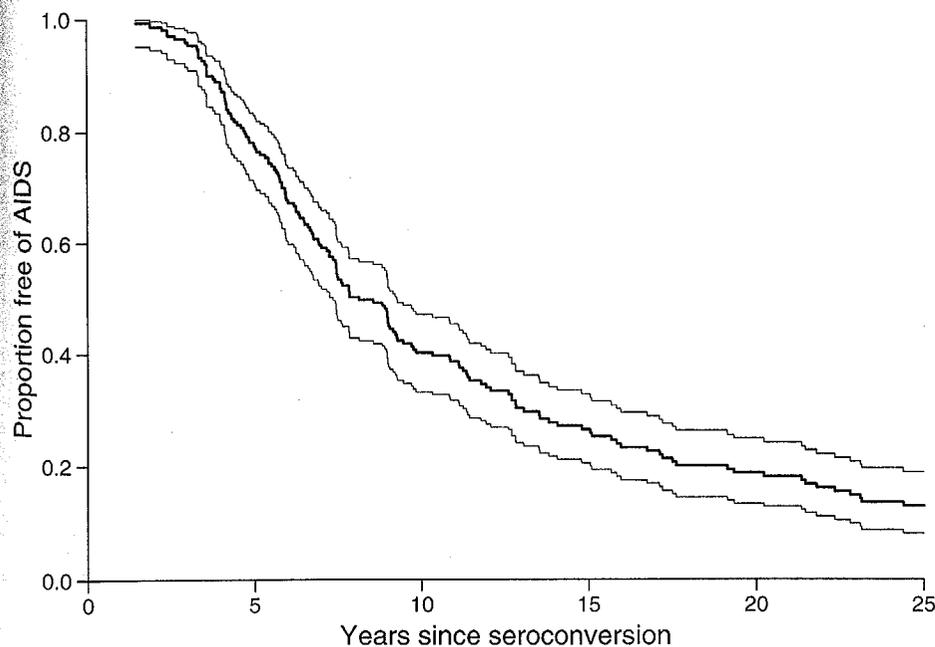


FIG. 3. AIDS-free survival in a cohort of 201 homosexual men from 1981 to 1995. Calculations were based on observed AIDS information and projected future AIDS cases based on CD4^+ counts.

TABLE 1. Kaplan-Meier estimates of proportions of persons surviving free of AIDS by years from seroconversion

Years from seroconversion	Proportion AIDS-free (95% CI)
5	0.78 (0.71, 0.83)
10	0.40 (0.33, 0.47)
15	0.26 (0.19, 0.34)
20	0.19 (0.12, 0.26)
25	0.13 (0.08, 0.19)

Estimates are based on both actual times of occurrence of AIDS and estimated times.

DISCUSSION

We observed a rapid increase in AIDS risk during the first years after seroconversion leading to a peak around year seven. During that year, AIDS-free subjects in our cohort had on average a 15% risk of being diagnosed with AIDS. The hazard rate fell modestly thereafter, but the study period was too short to evaluate subsequent trends in the hazard on the basis of direct data. However, when we included imputed times to AIDS derived by extrapolation from subject-specific CD4 trend lines, the risk appeared to stabilize at about 8% per year in subjects who remained free from AIDS for >10 years.

Overall, these findings are compatible with previous work as reviewed in the paper by Munoz et al. (14) using either parametric models for the incubation time distribution (15,16) or using the Kaplan-Meier estimator (17,18), as we did. To use this method, future times to

AIDS were imputed using random-effects linear models for the CD4 counts, thus extending previous work by Philips and Taylor, et al. (1,19). In this way, we were also able to evaluate the standard error of the imputed Kaplan-Meier curve as described in the Appendix.

The median time to AIDS (8.6 years) in the present study is in the lower end of the range reported by Munoz et al. (14) for homosexual and bisexual men. Nevertheless, it is probably close to the true estimate of the natural history of HIV infection for the following reasons: the cohort represents one of the oldest in the literature and most seroconversions were documented in the early part of the 1980s, long before any treatment for the disease was introduced. The impact of treatment is therefore considered very limited. Second, the follow-up was complete, that is, the Danish section of the cohort had 100% completeness and was based on a national mandatory reportable system of all diagnoses of AIDS.

Assuming that the extrapolation model is reasonable, the findings may be interpreted in several ways:

1. Theoretically, they could reflect the mixture of virus strains with different pathogenicity. However, this situation seems unlikely because the virus strains infecting our cohorts are probably highly homogeneous, in that most of the men became infected during the early 1980s.
2. The shape of the hazard function might largely reflect the introduction of primary prophylactic treatment. Although therapy undoubtedly has delayed development to AIDS and death in our subjects, it seems unlikely that the shape of the hazard would have been qualitatively different had therapy not been introduced. Thus, the study period does not include the most recently introduced protease inhibitors but only former treatment regimens that have been shown to postpone AIDS by at most 1 year. Furthermore, the effects of such treatments on CD4 level were limited, leaving little room for speculation that such treatment would significantly have changed CD4 trajectories. Therefore, with respect to the hazard seen in a closed cohort, such a treatment effect would tend to shift the curve to the right but would not substantially reduce the long-term cumulative hazard. Ideally, one could stratify the data on a calendar year basis to assess treatment effects. We found the hazard to be nearly unchanged in such analysis, but unfortunately this approach has little use in our setting because the seroconversion dates are relatively homogeneous.
3. Incomplete follow-up might affect the results. However, the observed hazard did not differ significantly between the two countries, and follow-up is particu-

larly complete in Denmark where the nationwide registries enable nearly complete ascertainment of vital status and disease events. In our study, all Danish participants were identified and carefully observed using these registries. The homosexual men in New York City and Washington, D.C. had follow-up through their private physicians and through direct correspondence with the research team; linkage with the cause-of-death registry was routinely performed.

4. A likely explanation for the shape of the hazard function in this cohort is that our subjects differ according to their ability to resist the consequences of infection. Recently, it has been demonstrated that the level of virus seen early in the course of infection is a strong predictor independent of age and CD4 status in relation to risk of AIDS (20,21). Subject-specific differences in viral load may reflect host genetic factors. Support for the existence of genetic restriction of progression to AIDS has been documented by Dean et al. (22). These investigators found that chemokine receptor 5 (CKR-5) deletion heterozygotes were significantly elevated in patients who survived HIV-1 infection for >10 years, in some cases twice as frequently as their occurrence in rapid progressors to AIDS. The same authors have reported the CKR-5 deletion allele to be present in 10% in the white racial group to which our cohort members belonged. Moreover, other groups have subsequently related chemokine receptors to disease progression (23,24). However, this impact may be small so that other factors should be taken into consideration to explain the results of this study.

To estimate the long-term hazard of AIDS in HIV-infected homosexual men, we chose clinical AIDS or a CD4⁺ count of 100 cells/ μ l as defining the presence of AIDS. Based on this conservative criterion, we found a total of 13% (95% CI, 8%–19%) of HIV-infected homosexual men to be free from AIDS after 25 years of HIV-seropositivity. An important aspect of the analyses was the ability to determine the variance of the Kaplan-Meier estimate by taking into account the extra uncertainty arising from the predictions even though this was not possible for the smoothed hazard curve in Figure 2B. This analysis showed that our predictions calculated up to 25 years after seroconversion had little influence on the variance of the Kaplan-Meier curve.

In conclusion, our natural history results suggest that certain mechanisms may confer substantial susceptibility to some individuals and substantial resistance to others. Indeed, our model suggests that $\geq 10\%$ of subjects in our cohort may ultimately survive >25 years AIDS-free.

Given the recent introduction of promising new therapies, we hope these estimates prove to be conservative.

APPENDIX

This appendix describes the estimation of the variance of the Kaplan-Meier estimator when some survival times free of AIDS are estimated with a given uncertainty. The data from which the Kaplan-Meier estimator $\hat{S}(t)$ is calculated consist of a number, k , of observed AIDS times:

$$X_1, \dots, X_k$$

and $n-k$ predicted AIDS times (some of which may be censored):

$$X_{k+1}^*, \dots, X_n^*$$

where each predicted time may be written as the sum:

$$X_j^* = X_j + \epsilon_j$$

of the true AIDS time, X_j , for that person, and an error term, ϵ_j , whose standard deviation, σ_j , is considered known from the linear model for the square root of the CD4 count (13). The variance of the Kaplan-Meier estimator based on the previous data can be expressed as:

$$\text{var}\hat{S}(t) = E(\text{var}(\hat{S}(t)|\bar{\epsilon})) + \text{var}(E(\hat{S}(t)|\bar{\epsilon}))(*)$$

where

$$\bar{\epsilon} = (\epsilon_{k+1}, \dots, \epsilon_n)$$

is the vector of error terms. The two terms on the right side of the equation are estimated by taking repeated samples of these error terms (i.e., by repeatedly sampling new terms from the normal distribution with mean = 0 and standard deviation = σ_j). We used 200 repeated samples of error terms for the estimation and for the h 'th sample, $h = 1, \dots, 200$, the available data were X_1, \dots, X_k and

$$X_{k+1}^* + \epsilon_{k+1,h}, \dots, X_n^* + \epsilon_{n,h}$$

For each data set, h ,

$$\text{var}(\hat{S}(t)|\bar{\epsilon}_h)$$

was calculated by Greenwood's formula for the Kaplan-Meier variance, and the average over the 200 samples then estimated the first term on the right side of the equation (*). Furthermore, the second term of (*) was estimated by the empirical variance of the 200 separate Kaplan-Meier estimates. Note that the number of uncensored AIDS times need not be the same for all samples (e.g., a prediction with a large variance may in some samples exceed 25 years, giving rise to a censored time).

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