Models of Survival in HIV Infection and Their Use in the Quantification of Treatment Benefits

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Because acquired immunodeficiency syndrome (AIDS) is a shifting endpoint and sufficient follow-up data now allow modeling of survival time (i.e., time from human immunodeficiency virus (HIV) seroconversion to death), the authors evaluated non-parametric and parametric models of mortality with the use of data from 554 seropositive participants in the Vancouver Lymphadenopathy-AIDS Study. The authors then applied these models to quantify treatment benefits at the national level in Canada, using back-calculation and forward-projection based on death registries. The study revealed that the lognormal model better describes survival time than the Weibull model. Relative to observations prior to 1987, later observations (in the era of treatment) revealed a statistically significant change in disease progression: the median survival time increased from 10.1 to 12.0 years, but no further survival improvements were observed in the early 1990s. Concurrent with the increase in availability of treatment, the authors have observed pronounced treatment benefits at the national level: prior to 1995, approximately 1,500 deaths were prevented and 4,200 person-years of life were saved. Also, mortality rates were observed to level off in the mid-1990s due to the shape of the historical HIV infection curve and the accumulating availability of treatment in Canada. Am J Epidemiol 1998; 148:487-96.

acquired immunodeficiency syndrome; age factors; back-calculation; HIV; mortality; projection; zidovudine

Studies of the natural history of the human immunodeficiency virus (HIV) infection have generally focused on time from HIV seroconversion to acquired immunodeficiency syndrome (AIDS) (incubation time) rather than time from HIV seroconversion to death (survival time), because the latter requires longer duration of study follow-up (1, 2). However, the study of survival time does offer advantages (1). AIDS is a shifting endpoint; its definition has changed over time as have diagnostic tools and knowledge regarding the AIDS diagnosis (3–5). As a result, notable changes in the incubation time have been reported from cohort studies (6–8). Progression to AIDS is reported to differ by transmission group but not when disease progression is evaluated in terms of immunologic marker paths and survival time (9–17). Thus, models of survival time may be less susceptible to confounding by transmission group. Death may also be a more meaningful endpoint for individual future planning and for economic evaluations. Finally, when using registry data, mortality data may be less susceptible to reporting delay and underreporting than AIDS case reporting.

Increasing duration of follow-up in ongoing cohort studies, now allows modeling of survival time. The non-parametric Kaplan-Meier method can provide insight into the risk of death during the period of observation, while parametric methods allow estimation of the risk of death beyond empirical observations. Models of mortality are not only important for the planning of observational studies and clinical trials, but are also crucial in reconstructing the historical HIV infection curve and forecasting future mortality trends. Such data provide insight into the dynamics of the HIV epidemic and are important for planning the provision of health services.

As early as 1989, cohort studies among homosexual
men reported alterations in the natural history of HIV infection as a result of treatment (18). Muñoz and Xu (19) reported an attenuation of the risk of AIDS in more recent years; for participants with CD4 cell counts of less than 100 cells/μl, the risk of AIDS was found to be reduced by 44 percent in 1988–1991 and by 49 percent after 1991, respectively, compared with the period prior to 1988. The authors attributed this at least in part to the availability of treatments. Hendriks et al. (20) applied Markov models based on CD4 cell observations, and estimated the median incubation time before March 1990 to be 7.6 years, and 9.6 years afterward. The latter date coincides with the availability of antiretroviral therapy and prophylaxis against opportunistic infections in this group. In contrast, Hessol et al. (21) reported an increase in the risk of AIDS after mid-1989 relative to earlier observations, and a slight, nonsignificant, reduction in the risk of death in more recent calendar years.

In this study, we first identify the best model for survival time in the Vancouver Lymphadenopathy-AIDS Study, a long-running cohort study of the natural history of HIV infection. Second, we apply this model when quantifying the beneficial effects of treatment in terms of reduction in the risk of death, as well as in terms of life gain, such as the number of deaths prevented and person-years saved at the national level in Canada.

MATERIALS AND METHODS

Cohort data

The Vancouver Lymphadenopathy-AIDS Study recruited 729 homosexual men between 1982 and 1984 and another 271 in 1986 and 1987 (22). A total of 408 were HIV-seropositive at study entry (i.e., seroprevalent) and 146 seroconverted under study (i.e., seroincident). Follow-up visits included medical inquiry by general practitioners, blood sampling for HIV antibody and immunologic testing, and behavioral questionnaires. Visits were scheduled at 3- and 6-month intervals until 1986, and annually thereafter. All observations obtained prior to July 1996 were included in the present analyses, and checked against local and national AIDS, death, and treatment registries.

The date of seroconversion was estimated through probability sampling using earlier models of the Canadian national HIV infection curve (23) and an individual’s seroconversion window (i.e., the period between last seronegative test and first seropositive test for seroincident individuals, and the period between January 1976 and the first positive visit for seroprevalent individuals). This method has been successfully applied and described in more detail elsewhere (24).

For the purpose of the present analyses, the appropriateness of the estimated seroconversion dates was checked by comparing the Kaplan-Meier survival curve of the 554 study participants, with the survival curve of the seroincident subgroup. Further, to omit survivorship bias, we left-truncated observations of all study subjects at the first positive visit. With respect to right censoring, we followed recently reported and discussed methods (2, 25, 26). Briefly, observations for individuals lost to follow-up (i.e., had no study visit in the last year—no visit after July 1995) were censored at the last visit, and individuals under follow-up (i.e., with a visit after July 1995) were censored as of July 1, 1996. Nine men died of non-HIV-related causes and were censored at their dates of death.

Analyses of cohort data: modeling survival time

For the purpose of providing an appropriate parametric model for the survival time, we followed the procedures recently reported by Muñoz and Xu (19) and applied for the incubation time. Muñoz and Xu considered three models: Weibull, lognormal, and a 3-parameter logistic model (see Appendix for formulae, and Muñoz and Xu (19) for a detailed characterization of these models). Weibull and lognormal models of the incubation/survival time are relatively simple and commonly applied. The 3-parameter logistic model is higher in hierarchy and allows mutual comparisons with the 2-parameter Weibull and lognormal models. These comparisons will reveal the statistical importance of the 3-parameter logistic model above the 2-parameter models, and also which one of the Weibull or lognormal best describes the data (see Appendix for likelihood function used). The procedure of maximizing the likelihood, and subsequently comparing these likelihood values over the three models, was repeated for 10 different sets of randomly assigned seroconversion dates, to show the consistency of these comparisons with respect to the seroconversion date estimates.

Non-parametric methods, Kaplan-Meier and Cox proportional hazard analyses, were used to confirm the findings of the parametric models and to test for differences in survival rates with respect to effectiveness of treatment and age at seroconversion (logrank test). With respect to effectiveness of treatment, survival rates of observations prior to 1987 were compared with those of observations after January 1987 (when treatment was made available for study participants) by left truncating the latter observations at this date (27). Parametric models based on observation prior to 1987 (pretreatment model), and observations after January 1987 (treatment model) are presented. Similarly, we investigated more recent time periods to assess the
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effectiveness of treatment strategies as they became available in the early 1990s.

National data

Since the early 1980s, deaths attributable to HIV/AIDS have been coded by Statistics Canada using the ninth revision of the World Health Organization International Classification of Disease (ICD-9) (28, 29). The first 10 deaths due to HIV/AIDS were reported in 1983. Then, from 1984 through 1994, the following numbers of mortalities were reported: 40, 145, 335, 525, 661, 851, 982, 1,170, 1,358, 1,564, and 1,628. A study conducted in 1991 (30) revealed underreporting rates of 10 to 20 percent. In the present study, we therefore upgraded the mortality figures by 15 percent and conducted sensitivity analyses to describe the uncertainties of the extent of underreporting, assuming no underreporting as a lower bound, and 30 percent underreporting as an upper bound.

In Canada, treatment, including antiretroviral therapy and prophylaxis against opportunistic infections, became available as early as 1987. Estimates from the British Columbia Drug Treatment Program revealed that in 1992, 50 percent of the HIV-infected individuals who had died had received treatment (31). As of 1996, this percent had risen to 90 percent (31). For the purpose of the present study, we assume a gradual increase in the proportion of deceased individuals who had received treatment beginning in January 1987, reaching 50 percent in January 1992 and 90 percent in January 1996. To describe the uncertainty in this assumption, we conducted sensitivity analyses, assuming that 90 percent of the deceased individuals would have had access to treatment by January 1995 and January 1997.

Analyses of national data: back-calculation, forward-projection, and treatment benefits

Back-calculation has become an established method to reconstruct the historical HIV infection curve from AIDS registry data, and has been described in detail elsewhere (32–35). Here we reconstructed the HIV
infection curve from mortality data. Treatment was considered by averaging the hazards of death according to the “pretreatment” and “treatment” models, considering the proportion of HIV-infected individuals having access to treatment. The Poisson function was used to maximize the likelihood. Second, starting with the reconstructed infection curve, we projected mortality rates for the actual situation (using both the “pretreatment” and the “treatment” models), and for the situation if treatment had not been available (using the pretreatment model only). The difference between these mortality rates represents the gain in survival as a result of treatment, and was expressed in terms of deaths prevented and person-years of life gained.

Back-calculation methods using AIDS registry data are imprecise with respect to recent infection rates because recent infections are not yet reflected in AIDS incidence (33). To a greater extent, this will be true for back-calculation based on mortality data, owing to a longer survival time. Also, back-calculation methods require strong assumptions about the shape of the infection curve which affects the incidence estimates. These limitations, however, apply to a much lesser extent to the outcome of forward-projections, which is our measure of interest. Nevertheless, we report on the outcome of forward-projections assuming three different, relatively simple models for the HIV infection curve. First, we applied the commonly used Weibull model for the infection curve, and subsequently, two other 2-parameter models, the logistic and lognormal, to investigate the variation in the outcomes of forward-projections resulting from the infection curve assumptions. Furthermore, we present the outcomes of projections with adjustment for differences in disease progression with respect to age (using three birth cohorts: born prior to January 1947, between January 1947 and January 1957, and afterward). Finally, we report the outcomes of projections incorporating distinct infection curves for transmission subgroups (the first one consisting of homosexual men, hemophiliacs, and other transmission groups, and the second consisting of intravenous drug users and heterosexual infected individuals).

RESULTS

By July 1996, 253 (45.7 percent) of the 554 seropositive study participants had died of HIV-related causes. Figure 1 gives the Kaplan-Meier survival curve and Table 1 provides additional descriptive statistics. The median survival time in this group was estimated to be 11.4 years (95 percent confidence interval [CI] 10.6-12.4). Figure 1 also presents the survival curve for the seroincident subgroup, which appears similar to that of the entire group.

Table 2 presents the maximum likelihood estimates of the 3-parameter logistic, lognormal, and Weibull models for 10 different sets of randomly assigned seroconversion dates. For each of these sets, the difference of the likelihood of the lognormal model with that of the 3-parameter logistic was not statistically significant, whereas the Weibull for each of these sets was statistically significant. Also, when restricting our

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**TABLE 1. Description of human immunodeficiency virus (HIV)-seropositive participants in the Vancouver Lymphadenopathy-AIDS* Study, 1982-1996**

<table>
<thead>
<tr>
<th>Category</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-seropositive participants</td>
<td>554</td>
<td></td>
</tr>
<tr>
<td>Enrolled in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wave 1 (1982-1984)</td>
<td>360</td>
<td>65.0</td>
</tr>
<tr>
<td>Wave 2 (1986 and 1987)</td>
<td>194</td>
<td>35.0</td>
</tr>
<tr>
<td>Seroincident individuals</td>
<td>146</td>
<td>26.4</td>
</tr>
<tr>
<td>Participants with AIDS diagnosis</td>
<td>325</td>
<td>58.7</td>
</tr>
<tr>
<td>HIV-related deaths</td>
<td>253</td>
<td>45.7</td>
</tr>
<tr>
<td>Median follow-up (years) of those still alive</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>No. under follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;January 1987</td>
<td>398</td>
<td></td>
</tr>
<tr>
<td>1987-1991</td>
<td>502</td>
<td></td>
</tr>
<tr>
<td>&gt;January 1991</td>
<td>392</td>
<td></td>
</tr>
<tr>
<td>Mean age (years) at seroconversion</td>
<td>30.6</td>
<td></td>
</tr>
</tbody>
</table>

* AIDS, acquired immunodeficiency syndrome.

**TABLE 2. Likelihood (-2 log-likelihood) of the 3-parameter logistic model and the deviance (probability) with the likelihood of the lognormal and Weibull models for 10 different sets of randomly assigned seroconversion dates in participants of the Vancouver Lymphadenopathy-AIDS* Study, 1982-1996**

<table>
<thead>
<tr>
<th>Seroconversion date set</th>
<th>3-Parameter logistic model</th>
<th>Lognormal model</th>
<th>Weibull model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-2 log-likelihood</td>
<td>Deviance (p)</td>
<td>Deviance (p)</td>
</tr>
<tr>
<td>1</td>
<td>1,793.62</td>
<td>0.4904 (0.5223)</td>
<td>8.1443 (0.0043)</td>
</tr>
<tr>
<td>2</td>
<td>1,792.70</td>
<td>0.4162 (0.5188)</td>
<td>8.2055 (0.0042)</td>
</tr>
<tr>
<td>3</td>
<td>1,793.58</td>
<td>0.3045 (0.5681)</td>
<td>8.8126 (0.0029)</td>
</tr>
<tr>
<td>4</td>
<td>1,793.15</td>
<td>0.3225 (0.5642)</td>
<td>7.5886 (0.0058)</td>
</tr>
<tr>
<td>5</td>
<td>1,793.25</td>
<td>0.2448 (0.6027)</td>
<td>8.8029 (0.0026)</td>
</tr>
<tr>
<td>6</td>
<td>1,793.87</td>
<td>0.3443 (0.5573)</td>
<td>8.5526 (0.0035)</td>
</tr>
<tr>
<td>7</td>
<td>1,794.35</td>
<td>0.3911 (0.5317)</td>
<td>8.4173 (0.0037)</td>
</tr>
<tr>
<td>8</td>
<td>1,793.35</td>
<td>0.3289 (0.5667)</td>
<td>8.2018 (0.0030)</td>
</tr>
<tr>
<td>9</td>
<td>1,794.78</td>
<td>0.4092 (0.5224)</td>
<td>8.2687 (0.0040)</td>
</tr>
<tr>
<td>10</td>
<td>1,794.95</td>
<td>0.4617 (0.4966)</td>
<td>8.4209 (0.0037)</td>
</tr>
</tbody>
</table>

Parameters:
- \( \beta_0 = -7.3969 \)
- \( \beta = 2.4442 \)
- \( \beta = 2.6053 \)
- \( \sigma = 0.4398 \)
- \( \sigma = 0.4398 \)

* AIDS, acquired immunodeficiency syndrome.
† The presented parameters used the average of 10 randomly assigned seroconversion dates as the starting dates (see text).
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analyses to the 146 seroincident individuals, the differences between the lognormal model and the 3-parameter logistic model was not statistically significant, whereas the Weibull was. The averaged estimates of $\beta$ and $\sigma$ for the lognormal model in these subgroup analyses (2.4438 and 0.6059, respectively) were close to the estimates for the group as a whole as presented in table 2.

The differences between the three parametric models is further shown in figures 2 and 3. The hazards of the lognormal and 3-parameter logistic models are similar and level off in the second decade of infection, whereas the hazard of the Weibull model increases monotonically. In terms of survival, differences between the models became pronounced after 12 years of infection. Twenty years after HIV seroconversion, the lognormal model estimated 19 percent to be alive, whereas the Weibull model estimated 9 percent to be alive.

In summary, in contrast to the Weibull model, the 3-parameter logistic and lognormal models appeared similar with respect to survival and model fit. Therefore, we use the relatively simple lognormal model for survival time in all subsequent analyses.

Observations after 1987 revealed a statistically significant reduced risk of death relative to earlier observations (table 3). However, no substantial changes were seen comparing observation prior to and after January 1991. We failed to demonstrate a change in the risk of death prior to and after January 1992, January 1993, and January 1994 (where more recent dates do not allow meaningful analyses). In our subsequent analyses, we therefore focused only on differences as observed prior to and after 1987. Younger age was also associated with slower progression rates, but the effect of treatment remained unchanged when adjusting for age (table 3). Figure 4 shows the lognormal survival functions for observations prior to 1987, and afterward. The median survival time using observations prior to treatment was estimated to be 10.1 years, whereas the median survival time was 12.0 years using observations in the era of treatment.

Using these models and Canadian national mortality data, we reconstructed the HIV infection curve for Canada (figure 5). Prior to 1990, approximately 28,000 individuals had been infected with HIV, which is consistent with outcomes from back-calculations on...
Years following HIV Seroconversion

**FIGURE 3.** Hazard of death following human immunodeficiency virus (HIV) seroconversion of 554 participants in the Vancouver Lymphadenopathy-AIDS Study.

the basis of AIDS surveillance data (35, and personal communication, C. Archibald, Division of HIV Epidemiology and Research, Bureau of HIV/AIDS and STD, Laboratory Centre for Disease Control, Health Canada, Ottawa, Ontario, 1997). Infection rates as shown after 1990 are unreliable because these infections are not yet reflected in mortality figures. Beginning with the HIV infection curve and using the lognormal models of survival time, we projected mortality rates. The projected mortality and reported mortality were very close and showed a leveling off in the mid-1990s (figure 5). The projected cumulative number of HIV deaths prior to 1995 was 10,659 (whereas the reported number was 10,660, considering 15 percent underreporting). If treatment had not been available, the total number of deaths would have been greater by 1,470 (figure 5). The number of person-years gained as a result of treatment was calculated from the area between both projections. From 1988 through to 1994, the numbers of person-years gained were 62, 128, 296, 520, 795, 1,085, and 1,357 each year. The cumulative number of person-years gained through January 1995 was estimated to be 4,243.

**Sensitivity analyses**

In the above results, we assumed 15 percent underreporting in the mortality figures. If we had considered no underreporting or 30 percent underreporting, cumulative number of person-years gained would have been 3,690 and 4,797, respectively. In addition, we assumed a gradual increase in the proportion of deceased individuals who had received treatment beginning in January 1987, and reaching 90 percent in January 1996. If this proportion had reached the 90 percent level in 1997, 4,173 person-years would have been saved, and 4,335 if it had been reached in 1995. To adjust for differences in disease progression with respect to age, we conducted the back-calculation and forward-projection separately for three birth cohorts (born prior to January 1947, between January 1947 and January 1957, and afterward). Compiling the results of the three birth cohorts, the total number of person-years saved was estimated to be 4,152. Similarly, we conducted the back-calculation and forward-projection for distinct transmission groups. Compiling these results revealed a total of 4,271 person-years
TABLE 3. Effect of treatment and age in 554 human immunodeficiency virus (HIV)-seropositive participants in the Vancouver Lymphadenopathy-AIDS* Study, 1982–1996, using univariate and multivariate Cox proportional hazard analyses

<table>
<thead>
<tr>
<th>Treatment, by year of observation</th>
<th>Relative hazard</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1987†</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1987–1991</td>
<td>0.449</td>
<td>0.227–0.890</td>
</tr>
<tr>
<td>≥1991</td>
<td>0.501</td>
<td>0.229–1.094</td>
</tr>
<tr>
<td>&lt;1987†</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1987</td>
<td>0.454</td>
<td>0.230–0.899</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25†</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>26–35</td>
<td>1.141</td>
<td>0.826–1.577</td>
</tr>
<tr>
<td>≥36</td>
<td>1.611</td>
<td>1.121–2.315</td>
</tr>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment, by year of observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1987†</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥1987</td>
<td>0.454</td>
<td>0.230–0.890</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25†</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>26–35</td>
<td>1.132</td>
<td>0.819–1.564</td>
</tr>
<tr>
<td>≥36</td>
<td>1.605</td>
<td>1.117–2.306</td>
</tr>
</tbody>
</table>

* AIDS, acquired immunodeficiency syndrome.
† Reference category.

saved. Lastly, assuming the 2-parameter logistic or lognormal models instead of the Weibull model for the HIV infection curve derived projections that were not substantially different. The cumulative numbers of person-years gained using the logistic and lognormal models were 3,924 and 4,213, respectively.

DISCUSSION

To our knowledge, this is the first study to report the benefits of treatments and health care on survival in HIV-infected individuals at the population level. Treatment results in a substantial lengthening of the survival time, and its availability in Canada led to a reduction of approximately 1,500 deaths and a life gain of 4,200 person-years prior to 1995.

We have quantified benefits of availability and access to treatments and health care at the population level. Whereas efficacy trials characterize drugs under well-defined study conditions, our quantifications of effectiveness answer health policy questions. They are the basis of cost-effectiveness evaluations and allow comparisons of benefits and expenses with those of alternative health care strategies and other health care problems.

Availability of treatment lengthens the median survival time from 10.1 years to 12.0 years. This is in agreement with findings of a lengthening in the incubation time in homosexual men by Muñoz and Xu (19) and Hendriks et al. (20). The latter estimated the median incubation time to increase from 7.6 to 9.6 years when treatment became available. While these authors failed to demonstrate a further increase of the incubation time in the early 1990s when more effective treatment regimens became available, we did so with respect to the survival time. These findings, however, do not include the recently reported effectiveness of triple combination treatment, including protease inhibitors, which had been introduced in Canada in 1994 on an experimental scale and since 1995 on a larger scale (36). Future analyses should reveal their effectiveness at the population level.

In addition to the incubation time, we demonstrated that the lognormal model better describes survival time than the Weibull model. For the purpose of future modeling of HIV infection, investigators should utilize lognormal models of the incubation and survival time. Relative to the Weibull model, the lognormal model estimates the risk of death to be substantially lower in the second decade of HIV infection, leading to higher proportions of individuals who survive despite long durations of infection. For example, we estimated 19 percent to be alive despite 20 years of infection. These figures are important for investigators focusing on so-called slow- or non-progressors, in order to gain an understanding of the disease and, if possible, to find clues for interventions (37–40).

Concurrent with the increase in availability of treatment, we have observed a strong increase in treatment benefits at the national level. The gain in life was most pronounced in recent years: The number of person-years saved increased from 795 in 1992, to 1,085 in 1993, and 1,357 in 1994. This number will likely further increase with the new regimens including triple combination treatment and protease inhibitors.

We have used documented resources of availability of treatment in Canada (31). Inaccuracies in this respect affect both the back-calculation and forward-projection of mortality. Sensitivity analyses, however, revealed that estimates were robust with respect to the quantification of treatment benefits. The documentation of availability of treatment can only be used for survival time evaluations, because it is not known whether the treatment was available prior to or after the diagnosis of AIDS. Given that we do not know at which stage of infection people were treated, we were not able to adjust for potential differences in this respect. We might have underestimated the sharp increase in treatment benefits if, over the years, infected individuals had extra benefits from receiving treatment in an earlier stage of infection.
Both the reported and projected mortality rates leveled off in the mid-1990s. Because these projections do not include the effectiveness of the newer treatments (triple combination treatment and protease inhibitors), this leveling off cannot be attributed to the benefits of these treatments, but should be interpreted as being the result of the shape of the historical HIV infection curve and the availability of mono- and double-combination therapy. However, the benefits of the newer treatments may become evident if it appears that the reported number of deaths in the next few years is substantially lower than the projected numbers presented here. Here, with the current approach, we have demonstrated the importance of considering the historical infection curve and availability of treatment at the national level, when drawing inferences from mortality rates.

Unlike the incubation time, survival time is not different for distinct transmission groups (9-17). Our survival models are therefore universally applicable. As applied here, back-calculation and forward-projection are not hampered by differences in disease progression between transmission groups. In addition, using mortality instead of AIDS data, calculations are not hampered by changes in the AIDS definition and the fact that persons may have AIDS but are not yet diagnosed and registered. However, underreporting, which occurs in both AIDS and death registries, affects the estimates of treatment benefits substantially. Using no underreporting or 30 percent underreporting as boundaries, we estimated the number of person-years gained to range between 3,700 and 4,800. Better insight into the extent of underreporting might improve the accuracy of our estimates.

ACKNOWLEDGMENTS

Support for the Vancouver Lymphadenopathy-AIDS Study is provided by an operating grant from the National Health Research Development Programme of Health Canada, through a National Health Scientist Award to Dr. Schechter, and National Health Research Scholar Awards to Drs. Hogg, Strathdee, and Montaner.
FIGURE 5. Annual human immunodeficiency virus (HIV) incidence and mortality rates in Canada. The presented reported mortality rates assumed an underreporting of 15 percent. For the reconstruction of the presented HIV infection curve, we used the lognormal model to represent the survival time, and assumed a Weibull model to represent the infection curve. The presented infection curve is the result of compiling the results of back-calculations of two transmission groups: one group consisted of homosexual men, hemophiliacs, and other transmission groups, and the second group of intravenous drug users and heterosexually infected individuals.

The study was conducted while the first author was a visiting postdoctoral fellow at the British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital, and the Department of Health Care and Epidemiology, University of British Columbia, Vancouver, British Columbia, Canada. This visit was financially supported by the Praeventiefonds, The Hague, The Netherlands.

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APPENDIX

Hazard of the 3-parameter logistic model:

\[ h(t) = \frac{1}{1 + \exp[-\beta_0 - \beta_1 \log t - \beta_2 (\log t)^2]} \]

Hazard of the lognormal model:

\[ h(t) = \frac{1}{\sigma \sqrt{2\pi}} \times \exp \left[-\frac{1}{2} \left( \frac{\log t - \beta}{\sigma} \right)^2 \right] \]

Hazard of the Weibull model:

\[ h(t) = \frac{1}{\sigma} \exp[-\beta] \times t^{\lambda \sigma} \]

Likelihood function:

\[ L(t) = \frac{h(t) \ S(t) \ S(t)}{S(\text{lag})(t)} \]

where \( h \) and \( S \) represent the hazard and survival at time \( t \), and where \( u \) and \( c \) refer to the uncensored and censored observations, respectively, and \( S(\text{lag})(t) \) the survival at the date of the first seropositive visit.