Methods for estimating the AIDS incubation time distribution when date of seroconversion is censored

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SUMMARY

In most cohort studies on HIV infection and AIDS, data on time from seroconversion to AIDS or death are doubly censored, both at the time origin and at the end point of interest. In epidemiological research, the most frequently adopted approach is to restrict the analysis to persons with narrow seroconversion intervals and to impute the midpoint of this interval as date of seroconversion. For many cohort studies, the consequence is that a substantial proportion of the data is not used.

We consider four methods that are expected to be less biased when all cohort data are used: two imputation methods, conditional mean and multiple imputation, and two likelihood maximisation methods. We derive the likelihood structure of the cohort data and clarify its dependence on study design. All methods are applied to data from the Amsterdam cohort study among injection drug users. In a simulation study the data generation process of this cohort study is imitated. Midpoint, conditional mean and multiple imputation are compared in performance. With midpoint imputation, both an analysis using the full data set, as well as one restricting to the cases with small seroconversion intervals, is performed.

Conditional mean imputation comes out as the preferred method. It gives best results with respect to mean squared error. Moreover, when confidence intervals are computed through standard methods that ignore the uncertainty in the imputed date of seroconversion, coverage probabilities are almost correct.
1. INTRODUCTION

An important research topic in studies on human immunodeficiency virus (HIV) infection and AIDS is the form of the distribution of time from seroconversion to either AIDS or death, and its dependence upon covariates. Often, data are obtained through cohort studies. Typically, some of the event data are right censored, due to loss to follow-up, death by competing risks or study cutoff.

Models for right censored data assume the origin of the relevant time scale to be known. However, the date of seroconversion is hardly ever known exactly. A cohort study may contain prospectively and retrospectively identified seroconverters as well as seroprevalent cases. Prospectively identified seroconverters have a last seronegative and a first seropositive test result, both obtained during follow-up. Seroprevalent cases were already seropositive at their date of entry into the study. Retrospectively identified seroconverters were also seropositive at entry, but have an earlier date at which they were known to be seronegative, e.g. through a test result obtained from stored blood samples. Moreover, cohort studies may contain persons who remained seronegative until the end of follow-up. So the date of seroconversion can be left censored, interval censored or right censored.

At the other end of the time scale, the date of AIDS occurrence or death may be right censored. However, interval censored dates of AIDS occurrence may be present as well. This is especially true if the first CD4 count below 200/µL is included in the AIDS definition, since CD4 counts are only measured at visits. Ignoring the interval censored nature, and considering the first measured CD4 count below 200 as AIDS event may lead to biased results.

Data which are censored both at the time origin and at the end point have been called doubly censored. Since most statistical packages currently only include models for right censored data, usually the midpoint between the last seronegative and first seropositive test is imputed as date of seroconversion. In most cohort studies, the majority of the participants is seen at least once a year, hence midpoint imputation can safely be applied to most prospectively identified seroconverters. However, retrospectively identified seroconverters usually have wider seroconversion intervals, and in many cohort studies seroprevalent cases outnumber seroconverters. Whether to include these persons in the analysis basically concerns a trade-off between bias and variance. If their number is high, inclusion of these persons considerably decreases variability in the estimate, which is further enhanced by the fact that this group often contains many early seroconverters with a long follow-up period. However, the decrease in variability should not be outweighed by an increase in bias through incorrect incorporation of the uncertainty in the date of seroconversion.

Several methods have been suggested that are expected to yield less biased results if seroprevalent cases and persons with wide seroconversion intervals are included. In this paper, four of these methods are considered in addition to midpoint imputation. By relating them to the general likelihood structure of the data and its dependence on study design, possible biases will be paid attention to. We restrict to nonparametric approaches. The methods are applied to data from an Amsterdam cohort study on HIV infection and AIDS. The methods that can be used fairly easily within the currently available statistical packages (all methods that impute a date of seroconversion) are compared in performance in a simulation study.
The main topic of interest will be the distribution of time from seroconversion for HIV type one (HIV-1) to AIDS. It will be called the incubation time. Since the data from the application do not contain interval censored event times, attention is restricted to right censored end points.

2. DOUBLY CENSORED DATA

With doubly censored data, two distinct time scales play a role. The date of seroconversion is measured on a calendar time scale, whereas the incubation time is measured on a scale relatively to the date of seroconversion (patient time scale). Let $N$ be the sample size. Without the inclusion of covariates, the relevant observable data consist of the set

$$
\{ (v^n_i, v^p_i, e_i, z_i, \delta_i, \gamma_i, \eta_i) \mid i = 1, \ldots, N \}.
$$

The date of study entry for person $i$ is $e_i$. The latest date he was known to be seronegative is $v^n_i$, and $v^p_i$ denotes the earliest date he was observed to be seropositive. If $v^n_i$ is not known, either we do not define $v^n_i$, or we let $v^n_i = \sigma_0$, with $\sigma_0$ denoting some common origin of the calendar time scale, like the assumed date of start of the epidemic. If he has not been observed to seroconvert, he is right censored with respect to seroconversion at $v^n_i$, and $v^p_i$ is not defined. We let $z_i$ denote the date of AIDS diagnosis, if observed ($\delta_i = 1$). Otherwise, $z_i$ is the date of last visit without AIDS, either for a person with a seropositive test result ($\gamma_i = 1$), or for a person who remained seronegative ($\eta_i = 1$). The variables $v^n_i$, $v^p_i$, $e_i$ and $z_i$ are measured in the calendar time scale, whereas $\delta_i$, $\gamma_i$ and $\eta_i$ are zero-one indicators, with exactly one of these taking the value one. Usually, more observation times are available, but they do not contribute to the likelihood. Hidden behind the observable data is the situation without censoring $\{ (x_i, t_i) \mid i = 1, \ldots, N \}$, with $x_i$ denoting the date of seroconversion and $t_i$ denoting the incubation time. Let the corresponding random variables $X_i$ and $T_i$ have distribution functions $G$ and $F$, with densities $g$ and $f$.

2.1. The likelihood structure

In deriving the likelihood structure, we make two assumptions:

1. The seroconversion and incubation time distribution are independent.

2. Conditionally on serostatus at entry, the observation times are independent of both the seroconversion time and the incubation time distribution.

The first assumption may be violated if there is any calendar time trend in incubation time, but can be corrected for by inclusion of calendar time as a covariate. The second assumption is conditionally on serostatus at entry, since usually an extra attempt to obtain observations before study entry is only made for persons who were seropositive at entry. This assumption may be violated if the first information after a seronegative visit is the occurrence of the event of interest. If this event occurs outside the normal range of visits, it induces an extra observation time. However, it can be corrected for by leaving these persons out of the analysis and correcting for
left truncation effects due to intermediate periods without observations (see below). It is unlikely to occur if the frequency of follow-up visits is high.

Some cohort studies allow both seronegative and seropositive persons to enter, whereas in others, enrolment is restricted to either of them. Cohort studies may have continuous enrolment of new participants (open cohort study), or persons may have been enrolled within a short period of time (closed cohort study). In some cohort studies, entry is restricted to persons who are AIDS-free. These different study designs influence the likelihood structure.

A derivation of the important part of the likelihood structure can be found in appendix A. First consider a closed cohort study. Then the time of entry \( E \) is fixed by study design. If entry is restricted to individuals who were seronegative at entry, the only role of the eligibility criteria \( EC \) in (A1), (A2) and (A3) in appendix A is to make \( G \) represent the seroconversion distribution, conditionally on being seronegative at time \( E \). The relevant part of the likelihood has the form

\[
N \prod_{i=1}^{N} \left[ \int_{v_{i}^{n}}^{v_{i}^{p}} g(s) f(z_{i} - s) ds \right]^{\delta_{i}} \times \left[ \int_{v_{i}^{n}}^{v_{i}^{p}} g(s) (1 - F(z_{i} - s)) ds \right]^{\gamma_{i}} \times \left[ 1 - G(v_{i}^{n}) \right]^{\eta_{i}}. \quad (1)
\]

In other types of cohort studies, \( EC \) induces a correction for left truncation effects via the inclusion of a denominator term. Its form depends on the type of cohort study and its enrolment criteria. First consider the situation that enrolment is restricted to persons who are AIDS-free. If both seronegatives and seropositives are allowed to enter, the probability to be eligible for enrolment at date of entry \( e_{i} \) is one minus the probability to have seroconverted and developed AIDS before this date. For each person a denominator term

\[
1 - \int_{\sigma_{0}}^{e_{i}} g(t) F(e_{i} - t) dt = \int_{\sigma_{0}}^{e_{i}} g(t) [1 - F(e_{i} - t)] dt + [1 - G(e_{i})]
\]

is added to formula (1). In cohorts, solely consisting of persons who were seropositive at entry, persons had to be AIDS-free and seropositive at entry. Hence, the correction term in the denominator has the form

\[
\int_{\sigma_{0}}^{e_{i}} g(t) [1 - F(e_{i} - t)] dt.
\]

If an open cohort solely consists of persons who were seronegative at entry, the correction term in the denominator becomes

\[
1 - G(e_{i}).
\]

Another correction for left truncation is due to intermediate periods without observations. Then, formula (2) applies, but with integration over the period from the date of last negative test to the date of first positive test.

Problems in the maximisation of the likelihood may arise if the enrolment criterion differs from the end point of interest: if death is the end point of interest, the \( F \) in the numerator refers to time to death, whereas the \( F \) in the denominator refers to time to AIDS. On the other hand, if AIDS is the end point of interest, and people only had to be alive in order to enter, no problems arise. By excluding persons who developed AIDS before entry, the entry criterion is brought in correspondence with the end point of interest.
In open cohort studies, the above formulas only apply if there is no change in relative sampling from seronegatives and seropositives over calendar time. Otherwise, the interpretation of $G$ depends on date of entry.

### 2.2. Methods for doubly censored data

Five methods will be discussed and compared. Methods EXP, RAN and LIK need an estimate $\hat{G}$ of the seroconversion distribution. Presented in order of computational complexity, these methods are

**MID: midpoint imputation.** For each person, impute midpoint between last negative and first positive test as date of seroconversion. Estimate incubation time via methods for right censored data.

**EXP: conditional mean imputation.** For each person, impute expected date of seroconversion, based on $\hat{G}$, conditionally on his date of last negative and first positive test. Estimate incubation time via methods for right censored data.

**RAN: multiple imputation.** For each person, impute date of seroconversion, based on a random draw from $\hat{G}$, and conditionally on his date of last negative and first positive test. Estimate incubation time via methods for right censored data. Repeat this procedure several times and average the results.

**LIK: maximum likelihood with fixed seroconversion distribution.** Maximise the likelihood in $F$ with $\hat{G}$ fixed.

**FULL: full likelihood procedure.** Maximise the likelihood with respect to both $F$ and $G$ simultaneously.

Methods MID, EXP and RAN are all based on imputation of a date of seroconversion, after which methods for right censored data can be used for estimation of $F$.

#### 2.2.1. Midpoint imputation

The magnitude of the bias of the midpoint imputation approach is determined by the incubation time distribution, the seroconversion distribution and the location and width of the seroconversion intervals. Since the median incubation time is about ten years, midpoint imputation yields fairly unbiased results as long as the vast majority of the seroconversion intervals has width smaller than two years. The influence of the location of the seroconversion intervals is through the form of the seroconversion distribution within these intervals. Midpoint imputation gives an unbiased estimate of the date of seroconversion if the seroconversion density is constant over the interval, even if the interval is wide. It will cause a bias towards a later (earlier) date of seroconversion if the seroconversion probability is decreasing (increasing) over the interval.
2.2.2. Methods based on separate estimate of seroconversion distribution

Methods EXP, RAN and LIK need an estimate of the seroconversion distribution for the cohort. Of course, data for this estimate need to come from a group that has the same characteristics with respect to the seroconversion pattern as the cohort itself (e.g. the same risk group). If the seroconversion data from the cohort itself are used, one option is to maximise

\[
\prod_{i=1}^{N} G(v^p_i)^{\alpha_i} \times \left[ G(v^p_i) - G(v^n_i) \right]^{\beta_i} \times \left[ 1 - G(v^n_i) \right]^{\eta_i}.
\] (5)

Here \(\alpha_i, \beta_i\) and \(\eta_i\) indicate whether the person is left censored, interval censored or right censored with respect to seroconversion. It corresponds with marginal likelihood maximisation in \(G\) if there were no truncation effects. If an open cohort only allows seronegatives to enter, truncation effects can be incorporated through inclusion of a denominator term \(1 - G(e_i)\) in (5). In the other types of cohort studies, we have to make some approximation since (2) and (3) require an estimate of \(F\). We assume \(F(e_i - t) \approx 0\), which is a reasonable approximation for persons entering near the start of the epidemic, when \(e_i - t\) remains small. If both seronegatives and seropositives are allowed to enter, this implies that (5) is used without an extra denominator term. In cohorts, solely consisting of persons who were seropositive at entry, a denominator term \(G(e_i)\) is added.

In the maximisation procedure, we iteratively switched between the EM-algorithm\(^{5,6}\) (expectation-maximisation algorithm) and the ICM-algorithm\(^{7,8}\) (iterative convex minorant algorithm), since this gives the highest speed of convergence. The estimate is not uniquely defined over the total range. On the parts with undefined values, which decrease in total length with increasing sample size,\(^{7,8}\) we choose the curve to be linear. Another approach for likelihood maximisation of interval censored data, as used by Hoover et al.,\(^9\) is not directly applicable here, since none of the event times has been observed exactly. However, the narrow seroconversion intervals could serve as exactly observed dates of seroconversion.

Conditional mean imputation (EXP) and multiple imputation (RAN) are general methods for missing data problems.\(^{10}\) After imputation, methods for right censored data can be used in the survival analyses. EXP has the practical advantage that only one imputed seroconversion date is needed for each individual, and the resulting survival estimates need not be averaged. A left truncation effect in the survival analysis is easily incorporated for right censored data.\(^{11}\) However, the same problems as explained in section 2.1 arise if death is the end point of interest, and people had to be AIDS free at entry. In method LIK, we impose the same piecewise uniform structure as in the full likelihood approach of section 2.2.3, and use the same SQP-algorithm\(^{12}\) (sequential quadratic programming algorithm). Computationally, it is a more complicated method than EXP and RAN.

Method EXP has frequently been used in incubation time studies.\(^{13–15}\) The method used in Hessol et al.\(^{16}\) is also based on the same idea, although the seroconversion distribution has been estimated differently.\(^{17}\) RAN has been used e.g. by Muñoz\(^{18}\) in a parametric model. The likelihood-based method LIK has been used by Gómez and Lagakos\(^{19}\) and Sun.\(^{20}\) In Bachetti and Jewell,\(^{21}\) the incubation time distribution is estimated in a way slightly different from method LIK.
2.2.3. Full likelihood for doubly censored data

Maximisation of the full likelihood leads to unstable results, since the likelihood can always be made infinite by choosing, for some \( k \) with \( \delta_k = 1 \), \( \hat{g}(s) = c/\sqrt{v_k - s} \), and \( \hat{f}(z_k - s) = c/\sqrt{v_k - s} \), on \( s \in (v_k - \varepsilon, v_k] \), and zero elsewhere. Therefore, we have to impose some structure. We assume \( G \) to be piecewise uniform on an equidistant grid \( \{x_0, x_1, \ldots, x_n\} \) and we assume \( F \) to be piecewise uniform on an equidistant grid \( \{t_0, t_1, \ldots, t_m\} \). We let both grids have the same binwidth \( \nu \). We choose \( \nu \) by visual inspection, taking into account the width of the seroconversion intervals. The resulting likelihood formula is derived in appendix B. This approach is somewhat similar to the weakly structured model in DeGruttola & Lagakos\(^2\) (their formula contains a rather crude approximation). Another, discrete approach has been used by DeGruttola & Lagakos\(^2\) and Tu.\(^22\)

The SQP-algorithm used\(^12\) checks whether the stationary point is a saddle point. The likelihood need not be concave on the allowed parameter space, especially when the grid size is small.\(^2\) Hence the algorithm may stop in a local maximum. Another problem is that time to convergence dramatically increases with decreasing binwidth.

Nothing is known about the asymptotic properties of the estimator, unless discrete distributions are assumed with a fixed number of mass points.\(^2\)

3. APPLICATION: THE AMSTERDAM COHORT STUDY AMONG INJECTION DRUG USERS (IDU STUDY)

The methods described above are applied to data from the Amsterdam Cohort Study among injection drug users (IDU study), containing a substantial proportion of persons with wide seroconversion intervals and seroprevalent cases (table 1). This study was started in December 1985. It is an open cohort study. Both seronegatives as well as seropositives, who were free of AIDS-defining conditions, have been enrolled. Only persons with Dutch nationality are included here, amounting to 637 persons at the date of analysis (January 1st, 1997).

Figure 1 depicts the seroconversion intervals for all 216 persons who ever tested seropositive during follow-up. The retrospectively identified seroconverters clearly have wider seroconversion intervals than the prospectively identified ones.

<table>
<thead>
<tr>
<th>WIDTH: number (percentage)</th>
<th>MEDIAN</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 yrs</td>
<td>&lt; 3 yrs</td>
<td>≥ 6 yrs</td>
</tr>
<tr>
<td>IDU-prev</td>
<td>57 (26%)</td>
<td>65 (30%)</td>
</tr>
<tr>
<td>IDU-ret</td>
<td>57 (64%)</td>
<td>63 (71%)</td>
</tr>
<tr>
<td>IDU-pros</td>
<td>52 (87%)</td>
<td>55 (92%)</td>
</tr>
</tbody>
</table>

Table 1: Width of seroconversion intervals for the IDU study. IDU-prev: total cohort; IDU-ret: all seroconverters; IDU-pros: only prospectively identified seroconverters. The seroprevalent persons are assumed to have been seronegative at 1/1/1980.
Figure 1: Seroconversion intervals for the Dutch injection drug users in the IDU study. Solid lines denote period between last seronegative test and first seropositive test for each person. Intervals are grouped by prospectively identified seroconverters, retrospectively identified seroconverters and prevalent cases without earlier seronegative test. The vertical ordering within the subgroups is determined by the midpoint date between each person’s last negative and first positive test.

In both LIK and FULL, the grid size is chosen to be 0.5 years.

The recruitment method is assumed to have been stable over time, although in reality there has been a shift towards less active recruitment from 1991 onwards, which may have led to a change in the relative sampling of seronegatives and seropositives. Assuming that there is no change in relative sampling, $G$ can be seen to represent the seroconversion distribution in the group of persons having Dutch nationality who satisfied the eligibility criteria at least for some period before the date of analysis. The estimates of the seroconversion distribution via the separate method (formula (5)) as well as via FULL are shown in figure 2. The amount of information as determined by the width of the seroconversion intervals is reflected in the
estimate. The wider intervals before 1986 yields a rather coarse estimate, having large jumps and long flat parts. Both curves and the conditional mean imputed date of seroconversion for

![Cumulative seroconversion distribution for the IDU study, obtained via the full likelihood method as well as via the separate method.](image)

**Figure 2:** Cumulative seroconversion distribution for the IDU study, obtained via the full likelihood method as well as via the separate method.

the seroconverters, based on the separate estimate (thick solid line), are summarised in figure 3. Since only the form of the distribution is important for imputation, seroconversion distributions are scaled to obtain the value one at the end of follow-up. The curves are quite removed from the intervals. This clearly shows that the prevalent cases and, to a lesser extent, the persons who remained seronegative also contribute to the estimate of the seroconversion distribution. Even if the survival analysis were restricted to the seroconverters, as in Gauvreau et al., the estimate of the seroconversion distribution cannot be based on the seroconverters alone.

In figure 4, the estimates of the incubation time distribution are depicted. AIDS diagnoses are based on the European 1993 AIDS definition. The curve for method RAN is based on 10 imputed sets of seroconversion dates. We also depicted what would happen in the “extreme situations”: assuming the date of seroconversion to coincide with the date of last negative test and first seropositive test respectively. The results from methods MID and EXP are very similar, probably due to the fairly symmetric distribution of the difference between midpoints and expected dates of seroconversion (not shown). Method RAN yields a slightly lower curve, especially for the first nine years. FULL has the lowest curve, and the curve from LIK is positioned in between RAN and FULL. The results obtained via FULL were dependent on the starting values of the algorithm. We chose four different sets of starting values. The differences in outcome were clearly visible (not shown). Only the curve with the highest likelihood is plotted. Also, using different binwidths yielded different survival curves. However, the tendency to yield a lower survival curve was present in all results from FULL. In the IDU study, truncation effects may
Figure 3: Cumulative seroconversion distribution for the IDU study, obtained via the full likelihood method as well as via the separate method. Curves are scaled to obtain the value one at the end date of analysis. The scale for these curves is given at the righthand side. The grey line depicts the imputed dates of seroconversion via method EXP. Only seroconversion intervals for the seroconverters are included as reference. Intervals are ordered by expected date of seroconversion.

be large. This may explain the different estimate from FULL. However, the result from method LIK, which uses the biased seroconversion estimate, also differs from the imputation methods. Moreover, if conditional mean imputation is used, based on the seroconversion estimate from FULL, the survival curve resembles the curve using conditional mean imputation based on the separate estimate obtained as in formula (5). Although FULL makes the fullest use of the data, all incorporated within one likelihood maximisation procedure, our piecewise uniform implementation may make it an inferior method for these data. Using a smaller grid will not solve this problem, since it will make maximum likelihood more unstable.

The Kaplan-Meier estimates obtained by assuming the date of seroconversion to coincide with the date of last seronegative test or the date of first seropositive test (the boundaries of the grey area), do not cover the other Kaplan-Meier estimates, and therefore can not be seen as truly extreme situations. Especially method EXP yields a curve which is higher on part of the time period. Truncation effects are the main cause of this phenomenon.

4. A SIMULATION STUDY

A striking result from the IDU data is that RAN yields a lower curve than MID and EXP. In order to get more insight into the quality and absolute performance of these three methods, we
Figure 4: Comparison of estimates of AIDS incubation time distribution based on data from the IDU study, using the five different methods. Shaded area gives area between Kaplan-Meier estimates obtained by assuming the date of seroconversion to coincide with the date of last negative test and first seropositive test respectively.

performed a simulation study, imitating the IDU study, and computed Kaplan-Meier survival curves. Note that estimation via these methods can be performed without much extra effort. The main difficulty is the estimation of the seroconversion distribution with interval censored data, which is currently not available in most statistical packages (S-PLUS 4.5 and higher being an exception\textsuperscript{25}). Once this estimate has been obtained, further estimation can be done using standard techniques for right censored data. In the simulation study, we also did the analyses restricting to seroconverters with a narrow seroconversion interval (less than two years), using midpoint imputation (method SCONV). Mean squared error is used as performance measure.

Data have been generated in the following way:

- With probability 0.45, a date of seroconversion is drawn from a shifted log-logistic distribution, starting in 1980. With probability 0.55, the date of seroconversion is unspecified, but later than 1997. So the seroconversion distribution on the period from 1980 until 1997 is given by

\[
P\{X \leq t\} = 0.45 \left(1 - \frac{1}{1 + (\lambda(t - 1980))^p}\right).
\]

We choose the location parameter \( \lambda = 10^{-0.8} \) and the scale parameter \( p = 2.5 \).

- The incubation time distribution is a shifted Weibull distribution, starting at one, having survivor function

\[
S(t) = \exp\{-((t - 1)/\lambda)^\alpha}\,
\]
with shape parameter $\alpha = 2$ and scale parameter $\lambda = 11$.

- Observation times are generated in the following way:
  Dates of entry are generated between 1986 and 1997 according to
  $$\mathbb{P}\{E \leq e\} = \sqrt{(e - 1986)/11}.$$  

After entry, visits are at regular half-year time intervals. With probability 0.25 two extra observation times $(U_1, U_2)$ before entry are available. $U_1$ is uniformly distributed between 1980 and $1980 + 0.75 \times (\text{date of entry} - 1980)$. $U_2$ is uniformly distributed between $U_1$ and $U_1 + 0.9 \times (\text{date of entry} - U_1)$. For seropositives, we assume complete follow-up until 1997 or AIDS diagnosis. Persons may leave the study before 1997 seronegatively. Dropout times are generated according to the same distribution as the entry times. If the dropout time is larger than the entry time and smaller than the date of first positive test, the person is right censored with respect to seroconversion at the date of dropout.

One thousand simulation runs have been done, except for the analysis with the restricted data set (SCONV), for which we generated 3000 data sets. Sample size in each run was 700. After deletion of the cases with an end point before the date of entry, on average 661 cases remained. The average number of cases with an observed seropositive test was 227; 49 of them were prospectively identified seroconverters, 33 retrospectively identified, whereas on average 55 cases had a seroconversion interval of width less than two years. In table 2, methods MID, RAN and EXP for the complete data set and method MID for the restricted data set are compared in performance with respect to bias, variance and mean squared error. 95% bootstrap confidence intervals are supplied as well. The curves for method RAN are based on 10 imputed sets of seroconversion dates. As is to be expected, the “safe” approach (SCONV) yields fairly unbiased estimates, especially during the first five years. Note that results at 7.5 and 10 years for SCONV are not completely reliable since we only use runs who had events after these time points. Method EXP does not perform much worse with respect to bias. With respect to mean squared error, all methods using the complete data set perform much better than SCONV, except for multiple imputation during the first five years. In general, EXP yields the best results.

### 4.1. Confidence intervals

In the simulation study, conditional mean imputation yields almost unbiased results. However, using standard methods for right censored data for computation of $p$-values and construction of confidence intervals may be problematic, since the uncertainty with respect to the imputed date of seroconversion is not incorporated. When there are many wide intervals, this may easily lead to incorrect assignment of significance to test results.

We computed coverage probabilities of the standard confidence intervals for right censored data (table 3). The low coverage probability at 2.5 years is caused by the large number of runs that do not have an event before 2.5 years. At later time points, coverage probabilities in method EXP and SCONV are almost correct. Note that confidence intervals for SCONV have been computed on the log-log scale, which performs best for small sample sizes. For EXP and
of is ignored, using the same kind of method based on interval censored data as in the estimation
plains this for a case who develops AIDS. This method can only be used easily if the dependency
we lose the independence between the observation time and event time distribution. Figure 5 ex-
between the date of first positive test and the date of last visit. However, by the transformation,
person who is AIDS-free at the end of his follow-up, is right censored at the time difference
interval censored incubation times in the patient time scale for a person who develops AIDS. A
scale before estimation. Interval censored seroconversion dates in the calendar time scale become
we approach one might think of, is to transform data from the calendar time scale to the patient time
We have considered five different estimation methods for doubly censored data. Another ap-
mid, the log-survival scale has been used. For SCONV, confidence intervals computed on the
log-survival scale have coverage probabilities 0.59, 0.91, 0.93 and 0.89.

<table>
<thead>
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<th>5</th>
<th>7.5</th>
<th>10</th>
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<td>2.71+3.96</td>
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</tr>
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<td>SCONV</td>
<td>−0.004+0.065</td>
<td>0.10+0.27</td>
<td>0.20+0.46*</td>
<td>2.35+2.80**</td>
</tr>
<tr>
<td>VARIANCE</td>
<td>3.28+3.60</td>
<td>11.7+12.8</td>
<td>14.9+16.2</td>
<td>15.4+16.8</td>
</tr>
<tr>
<td>RAN</td>
<td>2.54+2.31</td>
<td>8.68+9.54</td>
<td>12.4+13.3</td>
<td>13.6+14.8</td>
</tr>
<tr>
<td>EXP</td>
<td>2.74+2.44</td>
<td>9.80+10.7</td>
<td>15.6+17.1</td>
<td>16.3+17.7</td>
</tr>
<tr>
<td>SCONV</td>
<td>3.88+3.59</td>
<td>24.6+25.9</td>
<td>54.7+57.4*</td>
<td>105+112**</td>
</tr>
<tr>
<td>MSE</td>
<td>3.28+3.62</td>
<td>12.9+13.9</td>
<td>22.2+23.9</td>
<td>28.4+30.4</td>
</tr>
<tr>
<td>RAN</td>
<td>8.35+7.75</td>
<td>26.2+28.1</td>
<td>24.6+26.5</td>
<td>15.6+16.9</td>
</tr>
<tr>
<td>EXP</td>
<td>2.80+2.51</td>
<td>9.93+11.0</td>
<td>15.6+17.0</td>
<td>17.0+18.5</td>
</tr>
<tr>
<td>SCONV</td>
<td>3.88+3.62</td>
<td>24.7+26.0</td>
<td>54.7+57.5*</td>
<td>111+118**</td>
</tr>
</tbody>
</table>

Table 2: Comparison of methods MID, RAN and EXP using all available data as well as method MID restricting
the analysis to the persons having a seroconversion interval with width less than two years (SCONV). Estimates
of bias (expectation of estimated survival percentage minus true value), variance as well as mean squared error
(variance plus squared bias) are given, based on 1000 simulation runs for MID, RAN and EXP. For SCONV, we
used 3000 runs (*: based on 2966 runs; **: based on 1824 runs). 95% bootstrap confidence intervals are given as well.

MID, the log-survival scale has been used. For SCONV, confidence intervals computed on the
log-survival scale have coverage probabilities 0.59, 0.91, 0.93 and 0.89.

5. DISCUSSION

We have considered five different estimation methods for doubly censored data. Another
approach one might think of, is to transform data from the calendar time scale to the patient time
scale before estimation. Interval censored seroconversion dates in the calendar time scale become
interval censored incubation times in the patient time scale for a person who develops AIDS. A
person who is AIDS-free at the end of his follow-up, is right censored at the time difference
between the date of first positive test and the date of last visit. However, by the transformation,
we lose the independence between the observation time and event time distribution. Figure 5 explains this for a case who develops AIDS. This method can only be used easily if this dependency
is ignored, using the same kind of method based on interval censored data as in the estimation
of $G$ (section 2.2.2, formula (5)). Results are fairly biased (not shown). There is one situation
Table 3: Estimated overage probabilities of methods MID and EXP using all available data as well as method MID restricting the analysis to the persons having a seroconversion interval with width less than two years. Estimates are given, based on 1000 simulation runs for MID and EXP. For SCONV, we used 3000 runs (*: based on 2966 runs; **: based on 1824 runs).

<table>
<thead>
<tr>
<th>years after seroconversion</th>
<th>2.5</th>
<th>5</th>
<th>7.5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>MID</td>
<td>0.67</td>
<td>0.88</td>
<td>0.85</td>
<td>0.82</td>
</tr>
<tr>
<td>EXP</td>
<td>0.78</td>
<td>0.94</td>
<td>0.94</td>
<td>0.93</td>
</tr>
<tr>
<td>SCONV</td>
<td>0.55</td>
<td>0.96</td>
<td>0.96*</td>
<td>0.94**</td>
</tr>
</tbody>
</table>

Figure 5: Graphical representation of the time scale transformation with corresponding likelihood for an uncensored case, starting with the hidden space, in which all information is directly observable. We assume two observation times, \(U\) and \(V\), having density \(h\).

DATA

\[
\begin{align*}
  x, t & \quad \text{hidden data} \\
  z = (x+t), u, v & \quad \text{density: } \int_u^v g(s)f(z-s)ds \times h(u,v) \\
  (z_1, z_2, \{ z_1 < t \leq z_2 \}) & \quad \text{density: } \int_{z_1}^{z_2} f(s) p_{g,h}(z_1 - s, z_2 - s) ds \\
  \text{with } z_1 = x + t - v, & \quad \text{with } p_{g,h} \text{ the joint density of} \\
  z_2 = x + t - u, & \quad X - V \text{ and } X - U
\end{align*}
\]

in which neglecting the dependency leads to a true likelihood formula: if \(G\) is assumed to be uniform, and if there are no right censored data, then LIK yields the same formula.

We did not consider the inclusion of covariates. For the imputation methods, one can use standard regression methods for right censored data. Estimation of regression parameters in a proportional hazards model with doubly censored data has been treated in Kim et al.\(^{27}\) Another issue is whether a stratified estimate of the seroconversion distribution gives better results in the survival analyses. Since the shape of the seroconversion distribution is most important, the decision to make a split cannot be based on a test statistic like the log-rank. There is at least one stratification we do not advise: stratifying by seropositives at entry and prospectively identified seroconverters. Most seropositives at entry have their date of seroconversion earlier than the
prospectively identified seroconverters. However, there is no reason to assume a difference in HIV-incidence after the start of the study. Using one curve for the total cohort is preferable, since, being based upon a larger number of cases, it gives a more accurate estimate.

In the application to data from the Amsterdam cohort studies on injection drug users, results from all five methods have been compared. Survival estimates diverged to some extent. Our main conclusion from the simulation study is that conditional mean imputation gives almost unbiased estimates and that standard confidence intervals are almost correct. Multiple imputation yields estimates which are biased downwards. Using all cohort data is much preferable to the approach which only uses the seroconverters with narrow intervals. For our cohort, this even holds when midpoint imputation is used. For reasons of computational complexity, we did not include the likelihood maximisation methods in the simulation study. However, we obtained the result from the FULL likelihood in a few runs. Our impression is that, on average, it does not yield better results than method EXP with respect to the incubation time estimate, although the estimate of the seroconversion distribution is clearly better in the full likelihood approach. Further research on better implementations of the full likelihood method is needed, for example using a data adaptive binwidth or using a penalised likelihood approach. Using a reasonable parametric model will also overcome these difficulties (e.g. a lognormal distribution for the incubation time).

Of course, our conclusions cannot be generalised to all possible cohort studies. When very little or no information is available with respect to HIV-seroconversion for the period before the start of the cohort study, no accurate estimate of \( G \) over this period can be obtained from the cohort seroconversion data. However, from the simulation study we conclude that the around 30 retrospectively identified seroconverters from the IDU study already provide enough information. The full likelihood procedure, in which in principle information from \( F \) can be used to estimate \( G \), is unlikely to perform much better in this situation since the AIDS incubation time distribution is fairly flat. If there are doubts on the accurateness of \( G \), another approach may be to use marker values (like CD4 counts) at study entry to estimate individual seroconversion distributions \( \hat{G}_i \),\textsuperscript{28–30} using the seroconverters with narrow seroconversion intervals as reference group, or to use marker values as determinants of stages of disease progression in a Markov model.\textsuperscript{31} Data from the Amsterdam cohort studies, including the prevalent cases, have been analysed via the latter approach.\textsuperscript{32,33}

Another aspect that may lead to different conclusions in other cohort studies, is the influence of truncation effects. All methods using a separate cohort-based estimate of \( G \) ignore truncation effects in estimation of \( G \). If the amount of truncation is much larger than in the IDU study, FULL may perform best.

Even if conditional mean imputation yields almost unbiased results for some other cohort structure, standard confidence intervals may be too narrow. Then, bootstrap methods may perform better.

In order to obtain some insight into the quality of the methods for a specific cohort, we suggest performing a simulation study in which the data generation process of the cohort is imitated.
6. ACKNOWLEDGEMENTS

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REFERENCES


Appendix A. LIKELIHOOD CONSTRUCTION

Let $X$ represent the seroconversion distribution for the risk group of interest, and let $T$ represent the event time distribution for the same group. For each person, the following random variables are observed: $E$, the time of entry; $V = (V_1, V_2, \ldots, V_k)$, the (ordered) observation times (exclusive); possibly $V^n$ and $V^p$, denoting the date of last negative test and first positive test; $Z = \min\{X + T, V_k\}$, the (possibly right censored) event time; $(\Delta, \Gamma, H)$, the serostatus and event status at $Z$. The number of observation times $k$ may differ per individual. Let $EC$ be an abbreviation denoting that the person satisfied the eligibility criteria for inclusion in the study.

The observation times are split in the ones before and after entry: $V = (V^e, V_{\bar{e}})$. By assumption, $(X, T)$ is independent of the observation times distribution, conditionally on serostatus at entry. We derive the likelihood structure for a study design in which both seronegatives and seropositives are allowed to enter. If entry is restricted to either seronegatives or seropositives, serostatus is incorporated in $EC$ and the temporary inclusion of the event $X \leq e$ or $X > e$ is not needed. For a prospectively identified seroconverter, we have $v^n \geq e$, hence $X > e$ can be inserted in the likelihood. If the event is observed, hence $(\Delta, \Gamma, H) = (1, 0, 0)$, this person’s contribution to the likelihood is

\[ \mathbb{P}\{v^n < X \leq v^p, X + T = z | EC\} = \]
\[ \mathbb{P}\{v^n < X \leq v^p, X + T = z | X > e, EC\} \times \]
\[ \mathbb{P}\{X > e | EC\} \]
\[ \times \mathbb{P}\{(\overline{V}_e, E, V_{\bar{e}}) = (v^n, e, v^n) | X > e, EC\} \times \mathbb{P}\{X > e | EC\} \times \mathbb{P}\{(\overline{V}_e, E, V_{\bar{e}}) = (\overline{v^n}, e, \overline{v^n}) | X > e, EC\} \]

Note that for a prospectively identified seroconverter, $\overline{V}_e$ is usually empty, so $\overline{V} = \overline{V}_e$. For a retrospectively identified seroconverter or a seroprevalent case, we have $v^p \leq e$, hence $X \leq e$ can be inserted in the likelihood and a similar construction applies. The second term does not contain the distributions of interest, so it can be left out of the maximisation procedure, and we end up with

\[ \mathbb{P}\{v^n < X \leq v^p, X + T = z | EC\}. \quad (A1) \]

For a person who is right censored with respect to the event time, an analogous derivation applies, and the only important term for the likelihood maximisation is

\[ \mathbb{P}\{v^n < X \leq v^p, X + T > v_k | EC\}. \quad (A2) \]

For a person who is right censored with respect to seroconversion, the construction is even simpler, and we obtain

\[ \mathbb{P}\{X > v^k | EC\} \quad (A3) \]
as relevant term for the maximisation.
Appendix B. FULL LIKELIHOOD IMPLEMENTATION

Let the height of the distribution functions $G(x)$ and $F(t)$ in the grid points be denoted as:

$$
G(x_j) = \alpha_j \quad j = 0, \ldots, n \\
F(t_k) = \beta_k \quad k = 0, \ldots, m.
$$

Write $\alpha = (\alpha_0, \alpha_1, \ldots, \alpha_n)$ and $\beta = (\beta_0, \beta_1, \ldots, \beta_m)$.

Let $K_i$ denote the set of indices indicating which $t_k$'s are needed for the $i$-th individual,

$$
K_i := \{ k \mid z_i - v_{i}^p \leq t_k < z_i - v_{i}^n \} \cup \{ k \mid t_k < z_i - v_{i}^n < t_{k+1} \},
$$

and let $J_{ik}$ denote which intervals $[x_j, x_{j+1}]$ (partially) overlap $[z_{i} - t_{k+1}, z_{i} - t_{k}]$,

$$
J_{ik} := \{ j \mid \max(v_{i}^n, z_{i} - t_{k+1}) \leq x_j < \min(v_{i}^p, z_{i} - t_{k}) \} \\
\quad \quad \cup \{ j \mid x_j < \max(v_{i}^n, z_{i} - t_{k+1}) < x_{j+1} \}.
$$

Let $\theta_{ijk}^{(1)}$ denote the fraction of $[x_j, x_{j+1}]$ covered by $[\max(v_{i}^n, z_{i} - t_{k+1}), \min(v_{i}^p, z_{i} - t_{k})]$, and let $\theta_{ijk}^{(2)}$ denote the fraction of admissible values in the region $[x_j, x_{j+1}] \times [t_k, t_{k+1}]$. For $\eta_i = 1$, let $x_{j(i)}$ denote the first element larger than $v_{i}^n$, and let $\theta_{j(i)} = \frac{x_{j(i)} - v_{i}^n}{x_{j(i)} - x_{j(i)} - 1}$. For terms with $\delta_i = 1$, we add a term $\log(\nu)$. This can be seen as a penalty with respect to the grid on $F$ in the log-likelihood, if $\nu$ would be used as a free parameter in the maximization. Without truncation, the log-likelihood can be written as:

$$
\log L(\alpha, \beta) = \sum_{i=1}^{N} \delta_i \log \left[ \sum_{k \in K_i} \left( \beta_{k+1} - \beta_k \right) \sum_{j \in J_{ik}} \theta_{ijk}^{(1)} (\alpha_{j+1} - \alpha_j) \right] \\
+ \gamma_i \log \left[ \sum_{k \in K_i} \left( 1 - \beta_{k+1} \right) \sum_{j \in J_{ik}} \theta_{ijk}^{(1)} (\alpha_{j+1} - \alpha_j) \right] + \left( \beta_{k+1} - \beta_k \right) \sum_{j \in J_{ik}} \theta_{ijk}^{(2)} (\alpha_{j+1} - \alpha_j) \\
+ \eta_i \log \left[ 1 - \alpha_{j(i)} + \theta_{j(i)} \left( \alpha_{j(i)} - \alpha_{j(i)-1} \right) \right].
$$

(B1)

Truncation terms are included in a similar way. The likelihood is maximised in $(\alpha, \beta)$, using the SQP-algorithm (sequential quadratic programming algorithm).\textsuperscript{12}