# The incubation period of AIDS

Alvaro Muñoz, Caroline A. Sabin* and Andrew N. Phillips*

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## Introduction

A key epidemiologic descriptor of an infectious disease is the time it takes from infection to overt disease: the incubation period [1,2]. In this review, the origin from which the period starts being measured is determined by HIV-1 seroconversion, and the event that determines the end of the period is the occurrence of one of the clinical conditions defining AIDS (not simply having a CD4+ T-lymphocyte count $< 200\times10^6$/l) [3].

## Types of seroconverter studies

Cohort studies of HIV-infected individuals fall broadly into three main types: seroincident cohorts, seroprevalent cohorts with known seroconversion dates, and seroprevalent cohorts with unknown seroconversion dates. Strictly speaking 'seroconversion dates' are (almost) never known, but in cohort studies one can determine seroconversion intervals defined by dates of last negative and first positive tests. For this review 'known seroconversion dates' refer to cases in which both the last negative and first positive dates are known with corresponding intervals usually shorter than 1 year in length. The first two types of studies are often referred to as 'seroconverter studies' and the third as 'seroprevalent studies'. The value of and problems associated with seroincident and seroprevalent cohorts have been previously described [2,4]. However, further discussion of the different types of seroconverter studies is valuable.

### Prospective incident cohorts

HIV-negative individuals from a well-defined population are followed and seroconversions witnessed. Due to the low incidence of HIV-1 infection in most populations [5–8], these studies require substantial resources per HIV-positive subject, because a large group of individuals must be followed to identify the seroconverters, and those who agree to participate may not be representative of the population from which they are sampled. However, these are the only studies that provide the full natural history of HIV infection. Examples of studies such as these include the Multicenter AIDS Cohort Study (MACS) [9], the Amsterdam Cohort Studies of Human Immune Deficiency Virus Infection and AIDS among Homosexual Men [10] and Drug Users [11], and studies carried out among military personnel [12].

### Retrospective incidence cohorts

Members of these cohorts again come from a well-defined population, although seroconversions have occurred in the past. Studies of this type include cohorts of hemophilic individuals [13,14] and patients recruited into trials of the hepatitis B vaccine [5]. These individuals were carefully followed for reasons unrelated to HIV, and blood samples stored were retrospectively tested for HIV infection once a test became available. Since individuals who have not been seen may need to be tracked to obtain permission for testing stored samples, there may be many individuals with stored samples who cannot be contacted or who refuse to participate [6].

### Prospective prevalent cohorts with known dates of seroconversion

These cohorts opportunistically recruit new individuals with both a positive antibody test and a recent negative test. Unlike true incident cohorts, most patients are not under active follow-up prior to infection. However, these studies are more resource-efficient, in that they only involve follow-up of HIV-infected subjects, and therefore may be very large [15]. However, these studies often require the pooling of a large number of centers, with the intrinsic difficulty of assuring standardized procedures for the determination of seroconversions and clinical outcomes [16]. In addition, there is a potential problem with bias from this type of study, with patients with early HIV-related symptoms, who may develop AIDS more rapidly than other patients, presenting sooner after a negative test than those without symp-

From the Department of Epidemiology, The Johns Hopkins School of Public Health, Baltimore, Maryland, USA and the *HIV Research Unit, Department of Primary Care and Population Sciences, Royal Free Hospital School of Medicine, London, UK.

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Requests for reprints to: Dr Alvaro Muñoz, Department of Epidemiology, Johns Hopkins School of Public Health, Room E-7008, 615 North Wolfe Street, Baltimore, MD 21205, USA.

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toms. Those who perceive themselves to be at risk of HIV infection will be overrepresented in such cohorts, due to a tendency to seek serial tests.

### Retrospective prevalent cohorts with known dates of seroconversion

It is possible to retrospectively reconstruct a prevalent cohort of persons with known dates of seroconversion [17–19]. There is a danger of survivor bias, such that the probability of a person being included in the retrospective cohort is dependent on their vital status at a given time, with those who died soon after seroconversion being less likely to be included than those remaining alive [20]. In order to avoid this bias, it is essential that persons only contribute information to the incubation period estimates from the time of active follow-up (left-truncation or late entry). Clearly, the problems identified above with prospective prevalent studies are also relevant in retrospective studies.

## Methods to juxtapose prevalent and seroconverter cohorts

Seroconverter cohorts (i.e. with known dates of seroconversion) provide the most appropriate data for the estimation of the incubation period of AIDS. The nonparametric Kaplan–Meier method (or its extension to include truncation) has been the most widely used procedure for the estimation of the distribution of the incubation period of AIDS [14,16,21–23]. Due to the long incubation of AIDS, seroconverter cohorts must be followed for many years in order to accrue enough disease outcomes for reliable incubation period estimation. Prevalent cohorts (i.e. with unknown dates of seroconversion) require less follow-up to obtain a sizable number of clinical endpoints and are more readily available. In order to make use of prevalent cohorts for the estimation of the AIDS incubation period, procedures to determine the missing information on duration of infection prior to study entry are necessary. This has been undertaken in several ways by different investigators. In the first approach, imputation of the unknown duration of infection is based on the characteristics of the seroconversion curve of the population from which the study is drawn [24–29]. A second approach uses data at the individual level to determine how long the individual has been infected prior to entry into the study. A source of data is the history of sexual behavior that was likely to result in HIV infection (e.g. dates of sexual contacts with index cases) [30]. Another source of data is the observed times among seroconverters when certain values of markers that change after seroconversion occur. Under the assumption that the trajectories of the biological markers are similar to those observed in the incident cohort, the duration of infection in members of the prevalent cohort can be determined using their marker values provided at baseline [31,32]. The distribution of the incubation period can be estimated by the extension of the Kaplan–Meier method, incorporating truncation and standard error of the estimates should be computed using multiple imputation procedures [33]. Failure to incorporate truncation (i.e. adjustment for not observing all fast progressors) or complete lack of concurrently observing a subsample from the date of seroconversion will result in underestimation of the incidence of AIDS (i.e. overestimation of the median incubation period) [18]. Two important features of juxtaposing the incident and completed prevalent cohorts are that one cohort complements the other and due to elongation obtained by imputing the missing durations, information on the proportion AIDS-free at time periods longer than the duration of the study is attainable. Methodologically, these concepts are analogous to those in meta-analysis where one study supplements others and, therefore, one may refer to the methods reviewed here as 'juxta-analysis.'

The methods described above use markers of duration of infection observed in seroconverters to determine the missing durations of infection in the seroprevalent cohort. Conversely, one may use the sizable prevalent cohorts to develop a model for residual AIDS-free periods based on markers of disease progression. This leads to an alternative approach for juxtaposing prevalent and seroconverter subcohorts by determining the residual AIDS-free period of the censored observations in the seroconverter cohort. The imputation of residual AIDS-free periods is based on the values of prognostic markers at the last time individuals were seen [34]. This finding is of direct clinical importance in that it suggests that the short-term risk of AIDS is similar in those with the same CD4 count, even if they have been seropositive for different lengths of time [35,36]. Some limitations of these methods have been documented [37], but additional analyses [38] have supported the validity of the inferences.

The ranges of the estimates of the median of the incubation period of AIDS have been found to be 8.3–10.7 years in homo-/bisexual men [6,21,22,28,33,34,39–42], 10.2–11.6 years in injecting drug users (IDU) [18,23,32], and 12.6–16.5 years in hemophiliacs [13,14,43]. The differences in the estimates are probably mainly due to the heterogenicity of the incubation of AIDS according to the age at seroconversion (see below) and may also be due to differences in the spectrum of AIDS-defining conditions (e.g. Kaposi's sarcoma being common in homosexual men, but rare in IDU).

## Methods to incorporate incompleteness of outcome data

In most cohort studies, observation of the occurrence of the outcome of interest (e.g. AIDS) is not complete. Careful consideration should be given to the censoring

strategy in studies of the incubation period of AIDS. Censoring at the last time individuals were seen could lead to biased estimates if cases are actively sought and collected up to the date of the analysis [22,41,44]. Furthermore, if external sources of case reports are available, the level of ascertainment is improved and in the limit (i.e. complete ascertainment) it will be more appropriate to censor all those AIDS-free at the date of analysis [45]. Since for most studies the appropriate censoring strategy will be somewhere between the two extremes (i.e. at last time seen and at date of analysis), it is preferable to censor at the date of analysis AIDS-free individuals seen toward the end of the study (e.g. within 1 year of the date of analysis), and for the rest (e.g. those last seen more than 1 year before the date of analysis) at the date last seen [18,42]. It may also be necessary to consider those cases on whom the interval between the last time seen AIDS-free and the date of diagnosis is very long as censored at the last time seen.

Another mechanism that precludes the observation of the outcome of interest is the occurrence of an intermediate outcome, whereby the individual exits risk for the outcome (i.e., no longer at risk for the outcome of interest). In the context of AIDS, this is the case when pre-AIDS mortality is of substantial magnitude [46–49]. Since it is likely that those who had died would have soon developed AIDS had they not died, treating deaths from other causes as censored observations will result in an under-estimation of the hazard of AIDS. Alternative methods need to be used in the analysis of this type of data [50,51].

## Models for the incubation period

Parametric analyses of the incubation period of AIDS have been used to estimate the proportion of infected individuals who will eventually develop AIDS [52] and to implement back-calculation procedures [4]. Parametric regression models for the identification of factors explaining the heterogeneity of the incubation of AIDS are a useful alternative to Cox regression and provide a direct comparison of median values in different subgroups [53–55].

Using cohorts of seroconverters with observed follow-up durations of up to 6 years from seroconversion, several investigators have used the Weibull model for the incubation of AIDS [18,52,56,57]. Other investigators have found that although the hazard of AIDS increases during the first 6–8 years from seroconversion, the curvature changes and the hazard slows down and tends to flatten out [13,27,28,33,34]. This attenuation of the hazard is more consonant with the log-normal model being an appropriate distribution for the incubation period of AIDS. To decide which parametrization is more appropriate, it is necessary to have data on cohorts that have been followed for periods longer than the median incubation period [2,13] and to use hierarchial models that allow for likelihood-based hypothesis testing [58,59]. Using data on 2125 HIV-seropositive homosexual men with 1199 AIDS cases and a median follow-up after seroconversion of 10.7 years among the 926 AIDS-free men, it has recently been reported that the fit provided by the log-normal model was very close to that provided by a more general three-parameter logistic model [42]. Both the log-normal and the three-parameter logistic models were close to the non-parametric estimate and significantly better than the fit of the Weibull model. These findings were independently confirmed using data from the Tricontinental Seroconverter Study on 422 seroconverters whose median date of seroconversion was mid-1985 (P. Veugelers, personal communication, 1996). In this analysis, data from 153 AIDS patients were used, where those for whom the interval between the last time AIDS-free and the date of diagnosis exceeded 2 years were treated as censored.

The slowing of the hazard of AIDS for those who manage to remain AIDS-free for more than 10 years may well describe the natural history of HIV infection in the same way as for other infectious diseases [1,60]. However, in the case of HIV infection, it may also be due in part to the effectiveness of AIDS therapies and to misclassification errors resulting from imputation of unknown durations for the seroprevalent subcohort. Since the therapies generally available prior to 1996 were of limited and transient efficacy, it is unlikely that treatment plays a major role in explaining the attenuation of the hazard function of AIDS. In addition, the confirmation of the appropriateness of the log-normal model on the seroconverters from the Tricontinental Seroconverter Study makes it unlikely that the attenuation is due to misclassification error.

## Incubation period and age at seroconversion

In general, exposure group, sex and ethnicity differences in the incubation period are small [61,62] and can mainly be explained by factors such as differing access to care, the frequency of different AIDS-defining conditions in different risk groups or by age differences in the groups studied [17,23,49,63]. Although no differences by ethnicity have been reported, genetic factors associated with slow progression have recently been proposed [64,65]. Age is possibly the only cofactor that has been consistently shown to be associated with disease progression [12,23,61], especially in hemophilic patients in whom the age-range is widest [14,16,57,66].

Using semiparametric methods, several investigators have found that younger individuals had longer AIDS-free times, although the reported associations did not reach nominal levels of statistical significance [18,21,22,26,57].

Using log-normal regression methods on data from MACS [42], it has been shown that the effect of age at seroconversion is strongly significant ($P < 0.001$) and that the median incubation of AIDS (in years) in homosexual men is estimated by exp[2.2284 – 0.0133*(age at seroconversion – 30)]. Therefore, for a 10-year increase in age at seroconversion, the incubation of AIDS is reduced by the factor exp(–0.0133*10) = 0.875. These findings were independently confirmed using data on 232 AIDS-free and 88 AIDS patients among the homosexual men followed by the Italian Seroconversion Study (P. Pezzotti, personal communication, 1996). Specifically, using the log-normal model the estimated effect of a 10-year increase in age at seroconversion was exp(–0.0130*10) = 0.878, which was almost identical to the 0.875 provided by the MACS data. Fig. 1 shows these estimates of the median incubation of AIDS for different age values and the corresponding 90% confidence bands from MACS in comparison with estimates from other studies.

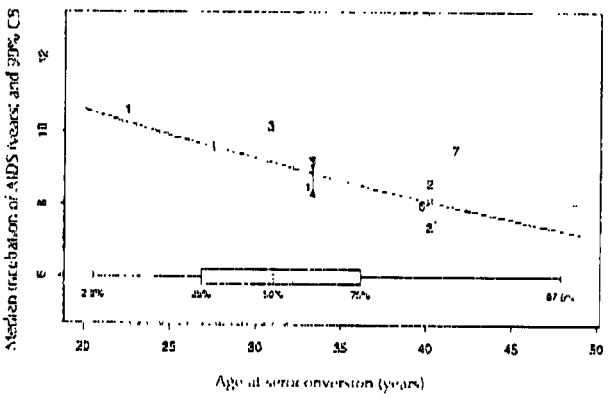


Fig. 1. Estimates of median incubation of AIDS in years for different age values and the corresponding 90% confidence bands (CB). Lines depict estimates and 90% CB of median incubation of AIDS by age at seroconversion based on the log-normal model and data from the Multicenter AIDS Cohort Study (MACS) [42]. The box-plot describes the distribution of the ages of those in MACS used for the estimation of the curves. The numbers in the graph depict estimates provided by other cohorts.1, Longini *et al.* [12]; 2, Rosenberg *et al.* [57]; 3, Hessol *et al.* [21]; 4, Veugelers *et al.* [22]; 5, van Griensven *et al.* [41]; 6, Pezzotti *et al.* [23]; 7, Darby *et al.* [14]. The '2's at age 40 years correspond to estimates under different models, and '4' and '5' are joined because they are estimates under different censoring strategies using the same cohort. It can be seen that after adjusting by the age at seroconversion, the agreement between different studies is fairly good, and that most of the differences are adequately explained by different cohorts having seroconverted at different ages. The deviations of '3' and '7' may be due in part to truncation and pre-AIDS mortality not being incorporated in the respective analyses.

## Early markers of disease progression

### Symptomatic primary HIV infection

Between 10 and 70% of individuals are reported to experience symptoms at the time of primary infection with HIV [67,68]. It has been suggested that the presence or extent of symptomatic infection may be associated with subsequent disease progression [69–72]. In one study of IDU, only 6.5% of those remaining asymptomatic at the time of seroconversion had developed AIDS by 4.5 years compared with 26.8% of those with symptomatic primary infection [68]. At the XI International Conference on AIDS (Vancouver, July 1996), Veugelers *et al.* [73] reported that of all evaluated symptoms, only individuals experiencing fever were at increased risk of AIDS; no other symptom was related to disease progression.

The explanation for a faster rate of progression in symptomatic individuals remains unclear. One suggestion is that the presence of symptoms may be related to a higher peak viral load at the time of seroconversion. However, while a number of studies [72,74,75] have reported viral load within the first 2 years after seroconversion to be related to progression, there is limited evidence that the peak of viral load experienced at the time of seroconversion is related to either the development of symptomatic infection or subsequent CD4 decline. This lack of evidence may relate to difficulties in measuring peak viral load levels in seroconverting individuals and to small numbers of individuals usually recruited into these studies.

### Markers soon after seroconversion

Whether viral or immunologic measurements in the short period after seroconversion are influential in determining the incubation period of HIV is of interest as this implies that clinical progression may be due in part to an individual's immunologic control of initial infection. RNA levels measured soon after seroconversion have been recently reported to be related to subsequent disease progression and CD4 decline [74–76]. However, other markers that have also been shown to be related to subsequent disease progression include the CD4 and CD8 lymphocyte counts [77], in particular the CD8+HLA-DR+CD38– subset [78], neopterin and $\beta_2$-microglobulin [79], and immunoglobulin A [77]. Whether these stay independently associated with disease progression after adjustment for RNA levels remains to be seen.

## Variations of incubation of AIDS by calendar period

Although clinical trials have demonstrated efficacy of several treatments for HIV-infected individuals, prior to 1996 their effects at the population level have not been large. Cohort studies have not shown a clear lengthening

of the incubation of AIDS over calendar periods corresponding to increasing levels of use of treatment at the population level [80,81]. The largest impact of therapies at the population level has been the change in the spectrum of AIDS-defining conditions [82–84].

Since different AIDS therapies have been introduced at different calendar periods, it is of interest to assess whether the hazard of AIDS in HIV-infected individuals has decreased with calendar year. Since the seropositive cohorts as a whole have aged and declined in the levels of the CD4 cell count, failure to adjust for the progressive immunosuppression of the cohort as a whole may result in later calendar periods showing a higher hazard of AIDS [21]. Similarly, although shorter incubation periods in cohorts of recent seroconverters are suggestive of higher hazard of AIDS possibly due to increasing virulence of the infectious agent, shorter incubation periods may simply be explained by the older age at which the cohorts seroconverted in comparison to prevalent cohorts that seroconverted at a younger age and in earlier calendar periods (i.e. confounding between age at seroconversion and calendar period) [85]. Furthermore, studies from large cohorts of homosexual men and IDU have documented that changes of immunologic markers at HIV seroconversion do not show calendar trends suggestive of increasing virulence [86,87]; and survival of AIDS-free HIV-infected individuals with CD4 cell counts of less than $350\times10^6$/l has been shown to improve since antiretroviral and HIV prophylactic treatments have become available [88].

When establishing the changes of the incubation period over calendar time, it is important to adjust by the overall level of immunosuppression and by the ages of the individuals at risk of disease at different calendar periods. Since it has been shown that given the CD4 cell count, the hazard of AIDS is not dependent on the duration of infection [35,36,38], the analysis simplifies to a Poisson regression stratified by CD4 cell count categories with age and calendar as categorical covariates [42]. Using this approach, the hazard of AIDS has decreased over calendar periods with increasing use of treatment in those with low CD4 counts [42,89,90]. Comparisons of the incubation period in the future must take into account the specific underlying treatment opportunities in the groups studied and analysis should adjust for known factors associated with progression and correlated with calendar period.

## Long-term non-progressors: a discrete group?

Whether long-term non-progressors (LTNP) are a discrete group who never progress, or whether they simply represent very slow progressors who will ultimately develop AIDS given enough time, has been the subject of debate [28,52,91–95]. While there is indication that behavioral or socioeconomic factors are not associated with long-term non-progression [94], evidence for both virologic and immunologic characteristics associated with LTNP is growing, including viral *nef* deletions [96], human leukocyte antigen class I alleles [97], and the recent suggestions of C-C chemokine receptor CKR5 Δ32 deletions [65]. While these studies point to both viral and host factors, the relative contribution of these factors in determining non-progression is still unclear. In fact, one-third to one-half of individuals identified as LTNP in large cohorts progress within 3–4 years [98,99]. One explanation may be the varying definitions of LTNP status currently used. Some definitions depend on a patient simply maintaining a high CD4 count and remaining AIDS-free for a certain period of time; others may further restrict LTNP status to those who have not experienced any decline in the CD4 count (i.e. a non-negative CD4 slope) over previous years. Comparison of definitions of LTNP status have shown that the choice of definition has a large impact on both the selection of individuals defined as LTNP and also on the stability of this patient group over time [100,101]. Definitions that do not incorporate a measure of CD4 decline are less stable and are more likely to include individuals who may progress over subsequent years than definitions that include this restriction.

Given our knowledge of CD4 decline and the relationship between the CD4 count and the development of AIDS, some studies have used CD4 patterns over the first years of the epidemic to project forward to estimate the proportion of individuals who will develop AIDS by 20 years from seroconversion [102]. Using this type of analysis, approximately 25% of infected hemophiliacs are expected to remain AIDS-free for over 20 years. In consonance with longer incubation in hemophiliacs (Fig. 1) these estimates are twice as high as those obtained from predictions based on models for the incubation period of AIDS in homosexual men [95]. As the use of more interventions with stronger effects continues to occur (e.g. combination of nucleoside analog drugs with protease inhibitors), it will be more challenging to identify the natural factors associated with long-term non-progression that may lead to further scientific insight.

## Summary

Given the effect of age at seroconversion on the incubation of AIDS, there is not a median incubation period but there are medians of incubation periods. In this review, we compared studies using the estimates of the median incubation of AIDS incorporating the differences in ages at the time of seroconversion in different cohorts. Previous reviews have compared studies using the cumulative incidence of AIDS at fixed durations of infection (e.g. 7 years) [2,28], and, as here, the variability

of the estimates may be explained largely by the ages at which different cohorts seroconverted. It is possible that the effect of age at seroconversion is stronger at younger ages (e.g. a quadratic effect of age) and the effect may attenuate at longer durations of infection (i.e. non-proportional relative percentiles [55]). Furthermore, several studies have shown that given the CD4 cell count in AIDS-free HIV-infected individuals, the lengths of time individuals have been infected do not provide significant additional information for the estimation of the residual AIDS-free time [35,36,38]. Therefore, it is likely that once CD4 is determined, age at seroconversion also provides less information. Indeed, for individuals with CD4 cell counts less than $200\times10^6$/l, the incidence of AIDS has been shown not to be significantly associated with age [42,103,104]. Among individuals with CD4 cell counts above $350\times10^6$/l, the hazard of AIDS is low, but older individuals are at relatively higher hazard of AIDS than younger individuals with similarly high counts of CD4 cells [42]. If both viral load and CD4 cell counts are known, the prognostic information provided by age is further diminished but not completely eliminated [105].

Here we have summarized the substantial advances in the modeling of the incubation period of AIDS, although further research is needed for the modeling of the time from seroconversion to death. When establishing the changes of the incubation period over calendar time, it is crucial to adjust by the overall level of immunosuppression/viral load, and possibly by the age of the individual at risk of disease at different calendar periods. Individuals of comparable ages who have decreased to a CD4 cell count below $200\times10^6$/l in calendar periods when AIDS therapies were available have been shown to be at lower risk of AIDS than those who did so at periods prior to the identification of efficacious treatments. Failure to adjust by immunosuppression/viral load and age may result in spurious associations and misleading effects of therapies or virulence of the infectious agent. Finally, the identification of LTNP is of great interest, and although it does not seem that they conform as a discrete group, their comparison with fast and moderate progressors may provide key elements to explain the considerably large variability of the incubation periods of AIDS.

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