Duration of time from onset of human immunodeficiency virus type 1 infectiousness to development of detectable antibody

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Background: For persons newly infected with the human immunodeficiency virus type 1 (HIV-1), the time from the onset of infectivity to the development of detectable HIV-1 antibody is unknown. Persons who donate blood during this period account for nearly all instances of HIV-1 transmission from HIV-1 antibody-screened blood transfusions.
Study Design and Methods: To estimate the window period from infectivity to HIV-1 antibody positivity, 701 HIV-1-seropositive blood donors who made a previous seronegative donation at 40 United States blood centers were studied. The HIV-1 antibody status was determined for at least one recipient of blood from the seronegative donation preceding the seropositive donation made by 182 of the 701 donors.
Results: There were 39 seropositive recipients of blood from these 182 donors. Three donors were excluded from further analysis because the seropositive recipients of their blood had other HIV-1 risk factors or had HIV-1 infection before transfusion. The final study population comprised the remaining 179 donors, of whom 36 (20%) transmitted HIV-1 infection to recipients. When the interval between the seropositive donation and the preceding seronegative donation was less than 180 days, 46 percent of the donors transmitted HIV-1. In contrast, when that interval exceeded 540 days, only 2 percent transmitted HIV-1. A mathematical model was developed to explain the relationship between the probability that the previous seronegative donation occurred during the donor's window period of infectiousness, and hence transmitted HIV-1, as a function of both the window period and the duration between the seropositive and previous seronegative donations. This model indicated that the transmission data were most consistent with an average window period of 45 days. Assuming a log-normal window period distribution, it was estimated with 95 percent certainty that at least 90 percent of persons had a window period of less than 141 days.
Conclusion: The window period averages 45 days, with few, if any, donors remaining infectious and seronegative for longer than 6 months. **TRANSFUSION** 1994;34:283–289.

Abbreviations: EIA(s) = enzyme immunoassay(s); HIV-1 = human immunodeficiency virus type 1.

SOON AFTER PERSONS are infected with human immunodeficiency virus type 1 (HIV-1), continuing virus replication produces high viral levels[1,2] and, consequently, a high level of infectiousness. During this time, some persons have demonstrable HIV-1 antigenemia or acute clinical symptoms.[3] Finally, measurable HIV-1 antibody develops. A critical period of unknown duration exists during which persons are infectious but are HIV-1 antibody-negative. The importance of this window period is demonstrated by the fact that nearly all instances of HIV-1 transmission from HIV-1 antibody-screened blood have resulted from donations made by newly infected persons during this period.[4] We studied HIV-1-seroconverting blood donors and the recipients of blood from their previous seronegative donation to determine the timespan from the onset of infectiousness and the ability to transmit the infection via transfusion of their blood to the development of HIV-1 antibody, which we will refer to as the window period of infectiousness (window period).

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Materials and Methods

Study population and data collection

Forty United States blood centers participated in the study. The study population consisted of all HIV-1-seroconverting

blood donors who made a seropositive donation before January 1, 1991, and who made at least one previous seronegative donation after March 1985. From shortly after March 1985 until the end of the study period, all donations at these centers were screened using HIV-1 whole-virus lysate enzyme immunoassays (EIAs). American Red Cross centers used EIAs manufactured by Abbott Laboratories (Abbott Park, IL) during the entire study period. The other participating centers used EIAs manufactured by Abbott Laboratories, Genetic Systems (Seattle, WA), Electro-Nucleonics (Columbia, MD), and DuPont (Wilmington, DE) during some or all of the study period. Repeatedly reactive donations were tested by Western blot and classified as seropositive if they showed bands of reactivity to at least one protein from each of the *gag*, *pol*, and *env* genes[5] (except at the New York Blood Center, New York, NY, during 1985 and early 1986, when only p24 and p41 bands were required).

When HIV-1-seropositive donors were identified, these blood centers attempted to collect information about the HIV-1 status of recipients of blood from the donor's previous seronegative donation. Because these investigations were only conducted on blood from persons with a reactive EIA and Western blot, for this study a person was considered to have HIV-1 antibody when he or she had both a reactive EIA and a positive Western blot.

The data included each donor's age and gender, dates of donations, types of components transfused, and the vital and HIV-1 status of the recipients of blood from the donor's last seronegative donation before his or her first seropositive donation. Because study data collection forms excluded personal identifiers and because investigations of recipients were not conducted specifically for this study, informed consent for our analysis was not obtained from donors or recipients.

General approach

Previous research indicates a nearly 100-percent virus-transmission rate to recipients of blood from infectious donors.[6-8] In another study, there were two recipients with known HIV status for each of seven donors. Each recipient pair had concordant HIV-1 antibody status.[9] This finding indicates a high probability of infection transmission by donors in the window period, as well as a sharply defined transition from noninfectiousness to infectiousness. Therefore, we assumed that the donor's blood was not infectious if at least one HIV-1-seronegative recipient was identified, even if all recipients could not be traced. Conversely, we assumed that the donor's blood was infectious if at least one seropositive recipient who had no other risk factors was identified. With these assumptions, we could establish whether a donor was infectious at the time of his or her seronegative donation by determining the HIV antibody status of recipients of blood from that donation.

The probability that the seronegative donation occurred during the donor's window period of infectivity, and hence transmitted infection to recipients, was related to both the duration of the window period and the length of time between the seronegative and seropositive donations (interdonation interval). If the average duration of the window period were long, there would be a higher probability that a donor's previous seronegative donation would have fallen within his or her window period. If the donor's interdonation interval were long, there would be a lower probability that the previous seronegative donation happened to fall within his or her window period.

We developed a mathematical model to describe the probability that a seronegative donation was made during the window period (and hence transmitted HIV-1) as a function of the both window period length and interdonation interval. With this model and the observed HIV transmission data on the seroconverting donors, we used the method of maximum likelihood to compute the average length and distribution of the window period.

Statistical approach

To construct a model for the HIV-1 transmission data conditional on a seropositive donation in the study period and the interdonation interval, we considered the time line illustrated in Fig. 1, representing a person who had made a seronegative donation at time T_1, who had made a seropositive donation at time T_2, and who had an (unknown) window period ω. We denote the interdonation interval $T_2 - T_1$ by ΔT, and consider initially the case where $\Delta T \geq \omega$. Let X be an indicator of whether transmission occurred at T_1 (X = 1 if transmission occurred, X = 0 if no transmission occurred). All probabilities are conditional on the donor's being seropositive at T_2.

The time T_{i-} denotes the *earliest* time that the donor could have become infectious. Since the donor is seronegative at time T_1, we deduce that $T_{i-} = T_1 - \omega$. If the donor had become infectious before T_{i-}, the donation at T_1 would have been seropositive, given our definition of the window period. The time T_{i+} denotes the *latest* time that the donor could have become infectious. Since the donor is seropositive at time T_2, we conclude that $T_{i+} = T_2 - \omega$. If we assume that the donor had an equal probability of becoming infectious at any time between T_{i-} and T_{i+}, then the probability that the donor was infectious at time T_1 is given by

$$p[X=1|\omega, \Delta T] = \frac{T_1 - T_{i-}}{T_{i+} - T_{i-}} = \frac{\omega}{\Delta T}, \quad \Delta T > \omega. \qquad (1)$$

Finally, if $T_2 - T_1$ is less than ω, then the probability that the donor was infectious at time T_1 is 1 (i.e., in this case, T_{i+} was before T_1). These probabilities are conditioned on the (unknown) window period. By introducing the (unknown) distribution of window periods into the model, we may calculate the probability that a donor who is seropositive at T_2 was infectious

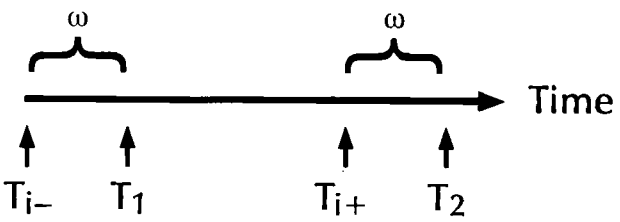

FIG. 1. Illustration of a donation time line for a hypothetical blood donor who made a seronegative donation at time T_1, made a seropositive donation at time T_2, and had an (unknown) window period ω. The window period is defined as the time from onset of infectiousness as a blood donor to the development of HIV-1 antibody. The time between the seropositive and seronegative donations, denoted as the interdonation interval (ΔT), is $T_2 - T_1$. Shown here is the case in which $\Delta T \geq \omega$. The time T_{i-} denotes the earliest time that the donor could have become infectious. Since the donor is seronegative at time T_1, we deduce that $T_{i-} = T_1 - \omega$. The time T_{i+} denotes the latest time that the donor could have become infectious. Since the donor is seropositive at time T_2, we conclude that $T_{i+} = T_2 - \omega$.

at time T_1, and this will be conditional only on the interdonation interval (ΔT). This probability is given by

$$p[X=1|\Delta T] = 1 - \int_0^{\Delta T} \frac{\Delta T - \omega}{\Delta T} p(\omega)d\omega \quad (2)$$

where $p(\omega)$ is the distribution of window times. In writing this probability, we have assumed independence between the times of HIV-1 infection and donation. Other research suggests that few seropositive donors donated so that they could be tested for HIV-1.[10] Donation for the purpose of testing would violate the assumed independence between times of donation and infection only if the time of donation was influenced by perceived possible exposures to HIV-1.

We next constructed the likelihood of observing the HIV-1 transmission data, conditional on the observed seropositive donations and the interdonation intervals. The log-likelihood, ℓ, for data $(X_j,\Delta T_j)$, where X_j was the transmission indicator and ΔT_j was the interdonation interval for the j^{th} of N individuals for whom recipient information was available, is

$$\ell = \sum_{j=1}^{N} X_j \ln p[X_j = 1|\Delta T_j] + (1 - X_j)\ln p[X_j = 0|\Delta T_j]. \quad (3)$$

We attempted to estimate the distribution of window periods by using maximum likelihood estimation. The maximum likelihood estimate of the window period distribution was concentrated at a single point, namely, 45 days. This finding suggested that window periods of those studied were relatively homogeneous, and that long window periods were unlikely. Data from donors with shorter interdonation intervals would have been required to determine the actual shape of the window period distribution; only one donor had an interdonation interval of less than 56 days, because the Food and Drug Administration mandates a minimum 56-day interdonation interval.

Our maximum likelihood estimate suggested that the interdonation intervals that we observed in our study were long, as compared with possible durations of the window period. We may use this observation as a simplifying assumption by considering a model in which there is a largest possible window period, ω_0 (defined such that all persons must have a window period shorter than ω_0). In this model, the probability of HIV-1 transmission as given in equation (2) for interdonation intervals longer than ω_0 takes the simple form $\bar{\omega}/\Delta T$, where $\bar{\omega}$ is the average window period. (For interdonation intervals less than ω_0, the probability of transmission depends on the specific form of $p[\omega]$, but it generally increases less rapidly with decreasing interdonation interval than $\bar{\omega}/\Delta T$.) This allows nonparametric estimation of $\bar{\omega}$, assuming only that interdonation intervals in our study are longer than ω_0. When we fit this model, the estimated average window period was 45 days (95% CI [34, 55 days]).

Because of changes implemented in the Abbott Laboratories EIA in March 1987, we also considered a model in which the window period changes at this date from ω_1 to $\omega_2 = \omega_1 - \Delta\omega$. As above, if there is a largest possible window period, ω_0, and if all interdonation intervals are long compared to ω_0, then it is possible to make a nonparametric estimate of $\bar{\omega}_1$, the average window period before March 1987, and hence $\bar{\omega}_2 = \bar{\omega}_1 - \Delta\omega$, the average window period after March 1987.

Table 1. *Reasons for nonrelease of seronegative blood for transfusion, 1985 to 1990**

	Number	Percentage
All donors	701	100
Total units not released for transfusion	140	20
Hepatitis B core antibody†	51	7
HIV EIA‡	38	5
Confidential unit exclusion§	28	4
Alanine aminotransferase	14	2
Rapid plasma reagin	3	0
Other reasons	13	2

* Study of 701 HIV-seroconverting donors at 40 US blood centers.
† Hepatitis B core antibody testing was implemented in US blood centers in late 1986 and early 1987.
‡ With or without an indeterminate Western blot.
§ The process by which potential donors can confidentially designate that their blood not be used for transfusion.

Results

We identified 701 donors who had seroconverted. Of these, 529 (76%) were men; their mean age was 32 years (range, 17-70). The seronegative donations from 140 (20%) of the 701 were not acceptable for transfusion (Table 1), and records for 3 donors were incomplete. The seronegative units donated by the remaining 558 donors (80%) had been released for transfusion, from which 959 components were made. We determined the HIV-1 status of at least one recipient of blood from 182 of the 558 donors. Information was unavailable on all recipients of components from 376 of the 558 donors, mostly because 412 recipients died of their underlying diseases before HIV-1 testing could be done. One hundred eighty-two donors gave seronegative units that were transfused to recipients on whom HIV-1 information was obtained; the recipients of 39 of these units were HIV-1-seropositive. Three of those donors were excluded from further analysis because for each there had been a single HIV-1-positive recipient who had documented HIV-1 infection or HIV-1 risk factors before the transfusion. Therefore, the crude HIV-1-transmission rate of the seronegative donation was 20 percent (36/179). For 23 donors, there were two recipients each with known HIV-1 status; in seven of these cases, the recipients were HIV-1 seropositive, and in 16, they were seronegative. This concordance among recipient pairs suggests the validity of our assumption that donors for whom there was one identified seronegative recipient did not transmit infection even if all recipients of that donation could not be found.

The HIV-1 transmission rate did not vary by the donor's age, gender, or type of component transfused, but it did vary by the time between the seronegative and seropositive donations, which we refer to as the interdonation interval (Table 2). For donors who transmitted HIV-1 infection, the median time

Table 2. *HIV-1 transmission by transfusion of blood from the most recent seronegative donation made by seroconverting blood donors according to the interdonation interval*

Interdonation interval (days)	Total	HIV-1 transmission	
		Number	Percentage
45-90	17	13	76
91-180	29	8	28
181-360	48	9	19
361-540	39	5	13
541-720	14	0	0
>720	32	1	3
Total	179	36	20

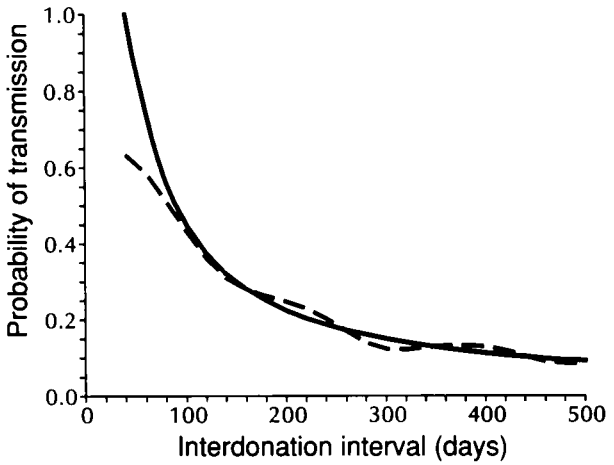

FIG. 2. Probability of HIV-1 transmission by blood from the last seronegative donation according to the time between that donation and the seropositive donation (interdonation interval). The dashed line is the observed probability of transmission (smoothed using kernel regression with a Gaussian kernel with a bandwidth of 45 days). The solid line is the predicted probability of transmission if the risk of transmission were the average window period (45 days) divided by the interdonation interval.

between seronegative and seropositive donations was 152.5 days, as compared to 369 days for those who did not.

The statistical analysis indicated that the window period of infectivity averaged 45 days and the distribution of window periods was narrow and relatively short compared to the distribution of interdonation intervals. Our model indicated that the probability that a seroconverting donor's previous seronegative donation fell within his or her window period, and hence transmitted infection to recipients, was the average duration of the window period divided by the interdonation interval. For example, with an average window period of 45 days, there would be a 10-percent probability (45/450) that a seronegative donation made by the same donor 450 days before a seropositive donation fell within the donor's window period of infectivity and transmitted infection to recipients.

In Fig. 2, the observed probability of transmission to recipients is plotted according to the interdonation interval. As also indicated in Fig. 2, the predicted probability of transmission, based on the relationship above, fits the observed data extremely well. We did not graph in Fig. 2 interdonation intervals greater than 500 days because only two transmissions were observed in 50 donations. However, the expected number of transmissions observed in the 50 donors was 2.9, assuming that the probability of transmission was 45 days divided by the interdonation interval. The good fit of this model to the observed probability of transmission over a wide range of interdonation intervals suggested that our estimate of 45 days for the average window period of infectivity was independent of assumptions about the distribution of window periods and depended only on the assumption that interdonation intervals in our study were relatively long compared to possible values of the window period. It also suggested that independence between times of donation and infection was a valid assumption.

Table 3. *95% CIs for the percentiles of the length of the window period**

Percentile	Days
95	0, 213.9
90	0, 140.5
75	0, 76.8
50	23.9, 56.6
25	10.9, ∞
10	5.2, ∞
5	3.3, ∞

* For example, with 95 percent confidence, at least 90 percent of seroconverting donors will have a window period of less than or equal to 140.5 days.

The Abbott EIA screening test was changed in March 1987 to make it more sensitive during early HIV infection. At the American Red Cross blood centers, all of which used the Abbott EIA during the entire study period, we found some evidence for a change in duration of the window period of infectivity, in that we estimated that with the earlier EIA to be 56 days and that with the modified EIA to be 42 days. However, the difference was not significant ($p = 0.26$, likelihood ratio statistic). Hence, for the remainder of this article we will assume that the window period did not change in March 1987.

Although our analysis indicated the distribution of window periods of infectivity was narrow, to determine the exact shape of that distribution would have required donors with interdonation intervals shorter than the 56 days required by the Food and Drug Administration. To determine if long window periods were consistent with our observed data, we assumed that the window period of infectivity followed a log-normal distribution. This was a conservative assumption because this distribution has a long "tail" and thus allows for the possibility that a few persons could have had very long window periods. If the distribution were log-normal, with 95 percent confidence, 90 percent of donors would have a window period of infectivity less than 140.5 days. Further details of the confidence limit analysis for the window period are in the Appendix and Table 3.

Discussion

These data indicate that the window period, defined as the time from infectiousness via the transfusion of donated blood to the development of HIV-1 antibody, averages 45 days. This estimate is independent of any distributional assumptions and depends only on most interdonation intervals in our study being long as compared with the possible range of window periods. Several studies have attempted to define the period from infection to antibody development by serial HIV-1 antibody testing of persons with a known date of HIV-1 exposure. While these studies have been limited by small samples, an analysis of the pooled results from these reports indicated that the median time to the development of detectable HIV-1 antibody was 2.1 months, with 95 percent of subjects developing antibody within 5.8 months.[11] Our 45-day average window period estimate from infectiousness to seropositivity was shorter than the median 2.1 months from infection to antibody development. If persons do not become able to transmit the infection via transfusion of their blood immediately after infection with HIV-1, we would expect the time from infection to antibody development to be longer than the

time from onset of infectiousness to antibody development. Finally, there is some evidence from our data that the window period with HIV-1 whole-virus lysate EIAs used after March 1987 averages only 42 days.

Another group of studies, using serially collected blood specimens from persons at risk for acquiring HIV-1, has employed DNA amplification or special serologic techniques to determine if persons remain HIV-1-seronegative in conventional HIV-1 antibody tests but have some evidence of infection for extended periods. While results from some of these studies were consistent with a median 2-month period to the development of HIV-1 antibody,[11-13] others have claimed that many persons do not produce detectable HIV-1 antibody for 6 months or longer.[14-16] The validity of results from some studies using DNA amplification techniques has been questioned.[17] Our data suggest that few, if any, persons remain infectious but seronegative for long periods of time, and our worst-case analysis supports those studies and case series demonstrating that newly infectious persons nearly always develop antibody within 6 months.

While it is possible that the distribution of window periods is bimodal and that a subpopulation exists of persons with very long window periods who make repeated, infectious but seronegative donations without being detected, this is unlikely for several reasons. First, our data collection spans more than 5 years, and, since our model accurately predicts the number of observed persons infected by blood from donations made at intervals longer than 500 days (2.9 expected vs. 2 observed), this subpopulation would have to have window periods longer than our data collection period. Second, the existence of a substantial group of blood donors with very long window periods would lead to the identification of numerous cases of AIDS acquired from HIV-1 antibody-screened blood donations. However, an exhaustive examination of persons reported with AIDS from April 1985 to March 1990 whose putative risk was transfusion found only 15 persons who actually acquired HIV-1 from an HIV-1 antibody-screened blood donation in the United States.[18] During this time, approximately 80 million blood components were transfused.[19]

We defined HIV-1 positivity as a reactive EIA and bands of reactivity on Western blot to products of each of the three major structural genes. Some newly infected persons will have a reactive EIA and a negative or an indeterminate Western blot before they develop a positive Western blot.[20-23] Therefore, the time needed to produce some measure of antibody reactivity (which would prevent the blood's release for transfusion) may average less than 45 days.

Our results were also based on EIAs used from 1985 through 1990. In early 1992, US blood centers began screening with third-generation double-antigen "sandwich" EIAs based on recombinant antigens for HIV-1 and HIV-2. Several studies indicate that these assays may be more sensitive than earlier whole-virus lysate-based EIAs in identifying persons with early HIV-1 infection.[24-26] This could be due to their ability to detect IgM antibodies, IgG antibodies (earlier detection), or antigen-antibody complexes. Therefore, the window period of infectivity for the third-generation antibody tests is probably less than 45 days. In several years, when sufficient numbers of donors are identified by the third-generation assays as having seroconverted, an analysis similar to that presented here can be done to determine the window period for these tests.

Our finding that the average window period of infectivity is short and that few persons have long window periods has several important implications. First, these data can be used to estimate the risk of HIV-1 transmission by antibody-screened blood.[27] Previous estimates were imprecise, largely because of uncertainty about the length of the window period.[28] Second, these data provide information about the expected outcomes of investigations of recipients of blood from seronegative donations made by donors who subsequently seroconvert. Table 2 shows the expected probability of finding a seropositive recipient on the basis of the interdonation interval. Investigations should be aggressively pursued when the interdonation intervals are less than a year. In addition, if a seropositive recipient is found, it is highly unlikely that additional seropositive recipients will be found to have received blood from donations made more than 6 months before the donation of blood that transmitted HIV-1. Finally, these data provide additional evidence that donors who have not engaged in high-risk behaviors within the 6 months previous to their donation are at low risk for being in the window period.

Appendix

To see how long a window period was consistent with our observed data, we performed a worst-case analysis. First, we assumed that the window period followed a log-normal distribution. We chose this distribution 1) because we expected that a window period of zero was impossible, and 2) because this distribution decays slowly to zero for large values of ω, which allows for the possibility that a few persons could have had very long window periods. The log-normal assumption required that there not be a mixture of two or more subgroups with disparate window periods. We then constructed worst-case upper 95% CIs[29] for the 50th, 75th, 90th, and 95th percentiles of the distribution of the length of the window period. We constructed a likelihood-based 95% CI for the parameters of the log-normal distribution. Out of all the distributions in this CI, we found the log-normal distribution that had the largest 50th, 75th, 90th, and 95th percentile, respectively. For example, all distributions in the 95 percent CI had a 90th percentile less than or equal to 140.5 days (Table 2); hence, we adopted (0, 140.5) as a one-sided 95 percent CI for the 90th percentile. A similar procedure was carried out for the 50th, 75th, and 95th percentiles. These results, shown in Table 2, suggest that window periods longer than 6 months are unlikely.

We also considered how short a window period was consistent with our data by constructing lower 95 percent CIs for the 5th, 10th, 25th, and 50th percentiles. In this case, we used the smallest 5th, 10th, 25th, or 50th percentile of all distributions as the lower 95 percent CI for that percentile.

To test the dependence of the confidence limits shown in Fig. 2 on the specific form of the log-normal distribution, we also constructed confidence limits assuming that the window period distribution follows a Weibull distribution. The Weibull distribution decays much faster for increasing window periods than the log-normal, and some Weibull distributions assign non-zero probability to window periods of zero. Using this distribution, we find the upper confidence limits for the 95th, 90th, 75th, and 50th percentiles are 194.2, 140.9, 82.7, and 58.6, respectively. The lower confidence limits for the 50th, 25th, 10th, and 5th percentiles are 24.5, 8.0, 2.2, and 0.8, respectively.

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