The probability of HIV infection in a new host and its reduction with microbicides

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We use a simple mathematical model to estimate the probability and its time dependence that one or more HIV virions successfully infect target cells. For the transfer of a given number of virions to target cells we derive expressions for the probability \( P_{\text{inf}} \) of infection. Thus, in the case of needlestick transfer we determine \( P_{\text{inf}} \) and an approximate time window for post-exposure prophylaxis (PEP). For heterosexual transmission, where the transfer process is more complicated, a parameter \( \gamma \) is employed which measures the strength of the infection process. For the smaller value of \( \gamma \), \( P_{\text{inf}} \) is from \( 6 \times 10^{-3} \) to 0.93 or from \( 7.82 \times 10^{-6} \) to 0.29, where the lower figures are for the transfer of 100 virions and the upper figures are for the transfer of 4.4 million virions. We estimate the reductions in \( P_{\text{inf}} \) which occur with a microbicide of a given efficacy. It is found that reductions may be approximately as stated when the number of virions transferred is less than about \( 10^5 \), but declines to zero for viral loads above that number. It is concluded that PEP should always be applied immediately after a needlestick incident. Further, manufacturers of microbicides should be encouraged to investigate and report their effectiveness at various transferred viral burdens.

1. Introduction

A comprehensive understanding and analysis of the early stages of HIV infection, including the process of transmission, is important as it may lead to efficient methods of reducing the probability that the virus successfully establishes itself in a new host. Such aspects of the population dynamics of HIV are relevant to the testing of preventive measures against the spread of the disease such as microbicides [1–5].

There are considerable and varied data on the probability that HIV will be transmitted per sex-act as well as by needlestick. For example, in a study of heterosexual transmission in monogamous couples in Uganda [6] the average rate of establishment of HIV in an uninfected host by contact with an infected individual was about 1 in 120 contacts (95% confidence interval 0.0039–0.0150) if the index or source partner had been infected for less than 2.5 months and about 1 in 670 (CI 0.0002–0.0007) if the index partner had been infected for periods from 6 to 15 months. A summary of seven sets of data in [7] gave an overall range from 0.0005 to 0.0026 for heterosexual HIV transmission probabilities. The use of microbicides is targeted at reducing these probabilities and so lowering the overall prevalence of the disease [5].

There have been several mathematical models for the growth of within-host HIV populations, many of which are deterministic, [8–12] whereas others have incorporated chance mechanisms [13–16]. Such models have provided valuable insights into the time-course of viral dynamics and the effects of drug therapy [10,12]. The matter of extinction of an HIV population in a new host also has been raised by some authors [15,16]. Here, we wish to address quantitatively one of the factors involved in the establishment of HIV in a new host: namely the success or failure of invading virus particles to reach and infect CD4+ T-cells or other susceptible targets.

There are many factors contributing to the stochastic nature of the success or failure of the establishment of an HIV population in a new host. Nevertheless, there must be firstly a transfer of one or more infectious viruses at a point or region of first contact. According to [17], the infectivity of virions may be decreased as neutralizing antibody responses develop and hence may depend on the time since transfer to a donor, in accordance with the data on the probability of transmission relative to the time of encounter between host and donor [6]. The virus must survive in the new host until it reaches and then infects CD4+ T-cells, and then it must not go extinct [15,16]. We are primarily concerned with the second stage of this sequence of events. It is not known with certainty whether free virions, cell-bound virions, or infected cells are involved in the infection process [7], but for simplicity we assume that a certain number of virions are physically transferred to a new host without distinguishing whether they are free or cell-bound. We first consider the case of needlestick transfer and then heterosexual transmission.
2. Model description

Suppose that \( n \) possibly infectious virus particles are transferred to an uninfected potential host as the result of contact with an infected individual. The value of \( n \) is extremely variable and depends on the state of the infected source and to a large extent on the mode of transmission. For needlestick transfer we estimate values of \( n \) below. For male–female sexual transmission the number of virions transferred can be from about 50 to several million [7].

Assume that \( n > 0 \) virus particles have reached a viable environment containing target cells (for example, uninfected CD4+ T-cells or macrophages) and that the clearance rate of the virus particles is \( c \) per day [18]. For each virus particle there are two possibilities, either that it will not survive long enough to successfully infect a T-cell or it will find a target before it is cleared. The probability that any virus will not survive throughout any small time interval of length \( \Delta t \) is very close to \( c \Delta t \). The process in which organisms either die or survive is called a pure death process. In accordance with the properties of this process, the probability that a virus survives for a time interval of length \( t \) is given by \( \exp[-ct] \) [19]. The probability that a virus introduced into the body at time \( t = 0 \) survives and infects a target cell in the time interval \((t, t + \Delta t)\) is thus \( p = kT \exp[-ct] \Delta t \), where \( T \) is the density of target cells and \( k \) is the target cell infection rate per virion [13]. For \( n \) invading virions we assume that new infections occur according to a Poisson process with rate \( p_n = np \). From the theory of inhomogeneous Poisson processes [20] we find that the probability that at least one of the \( n \) entering virions infects a target cell before time \( t \) is thus

\[
P_n(t) = 1 - \exp\left[-\left(\frac{knT}{c}\right)(1 - \exp(-ct))\right],
\]

and the probability that at least one target cell is ultimately infected is

\[
Q_n = 1 - \exp\left[-\frac{knT}{c}\right].
\]

The probability that no target cell is ever infected is \( 1 - Q_n \). Note that this result also follows directly from the Poisson distribution.

The average number of target cells a virus infects during its lifespan is \( kT/c \), where \( kT \) is the number of target cells infected per unit time and \( 1/c \) is the average lifespan of a virus particle. Thus, \( n \) virions on average infect \( nkT/c \) cells and the probability that no target cell is infected is \( \exp[-nkT/c] \). Furthermore, the probability that the time of infection of a target cell is later than time \( t \) is

\[
S_n(t) = Q_n - P_n(t).
\]

After a target cell is infected, that cell will produce virus which then may infect other cells. Note that after a virus has infected a host cell it cannot infect other cells as it is absorbed into the infected cell.

Using terminology from epidemic theory, the average number of other cells that one cell, infected by a virus, placed in a population of target cells ultimately infects is called the basic reproductive number, \( R_0 \). Stafford et al. [21] estimate from primary infection data in humans that \( R_0 \approx 5.7 \). Thus, the probability that one infected cell will infect one or more other target cells is \( 1 - \exp[-R_0] = 0.997 \) [22], so it is highly likely that once one target cell is productively infected, the infection will continue to propagate. This implies that the probability of infection of a new host is very close to \( Q_n \).

3. Results

To illustrate the use of the above model in estimating the probability of infection for various numbers of transferred infectious virions, we show in Fig. 1 the probability \( Q_n \) versus \( \log_{10} n \) for various parameter values. The value of \( T \) is set at 1000/mm\(^3\). The values of \( c \) label the two subplots, in each of which there is a curve for \( k = 2.7 \times 10^{-4} \) mm\(^3\)/day (red, upper curve) corresponding to a highly infectious virus and \( k = 6.5 \times 10^{-5} \) mm\(^3\)/day, (blue, lower curve), for a substantially less infectious virus. Precise values of \( k \) are not known. Perelson et al. [23] estimate that the diffusion-limited rate of encounter of a virion with a target cell is \( 8.6 \times 10^{-3} \) mm\(^3\)/day. Each of these encounters does not infect a cell, both because each virion is not infectious and because some

![Fig. 1. The probability that infection ever occurs is plotted against the logarithm of the number of invading virus particles in a potential host. The parameter \( c \) which labels the upper and lower subplots is the virus clearance rate. For the red (upper) curves, \( k = 2.7 \times 10^{-4} \) and for the lower (blue) curves \( k = 6.5 \times 10^{-5} \). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)](image-url)
encounters may be too short to lead to virion binding. If one in a hundred encounters were productive, then \( k = 8.6 \times 10^{-5} \text{ mm}^3/\text{day} \).

The value of the virion clearance rate constant \( c \) has never been estimated in acute infection. For a group of four chronically infected patients \( c \) has been estimated as 23 day\(^{-1}\) [18] (see also [24]). Since clearance could be elevated once seroconversion occurs, we have examined two values of \( c \) about 10-fold apart, \( c = 23 \text{ day}^{-1} \) and \( c = 2 \text{ day}^{-1} \). Fig. 1 shows that for the smaller clearance rate, \( c = 2 \text{ day}^{-1} \), the probability of infection becomes close to one for \( n \) in the range 20–100, whereas when the clearance rate is \( c = 23 \text{ day}^{-1} \), \( Q_n \) is close to one for \( n \) in the range 300–3000. Here, it has been assumed that all virions have access to target cells and that the virus does not go extinct in the new host. This scheme is modified below.

We also determine the percentage reduction in probability of infection when the number of transferred virions is reduced from \( m \) to \( n \). This can be obtained from the formula for \( Q_n \) above as

\[
R_m = \frac{(Q_m - Q_n)}{Q_m} \times 100\%.
\]

For example, using this simple formula, if \( c = 10 \text{ day}^{-1} \) [18], \( k = 2.7 \times 10^{-4} \text{ mm}^3/\text{day} \) and \( T = 1000 \text{ mm}^3 \) [8], reducing the initial number of virions from 100 to 5 gives an 86% reduction in chance of infection, whereas a decrease from 100 viruses to 50 gives a 21% reduction. More examples are given in Table 1. These calculations again assume that transmission is direct. In the next two subsections we consider in more detail the transfer of virus particles by needlestick and by sexual intercourse.

### 3.1. Needlestick transfer and post-exposure prophylaxis (PEP)

The transfer of HIV by needlestick, for example in health-care workers, is conceptually simpler than transfer of the virus by sexual intercourse. In the absence of an accurate way to assess how many virions act as a source for the new infection, we estimate that the total number of virions in the transferred volume of blood, which gives the worst-case scenario for infection, is in the range 100–500. This gives an indication of the number of transferred virions, being only of the order of an hour or less. This is the case when the source of blood is from an acutely infected person. If the source person is not in an acute phase, then the time interval is much longer, being up to several hours or of order a few days if the viral clearance rate is low. It is of interest to try to relate these results to the time window for effective PEP [26], but this aspect is complicated by the role of latently infected cells, whose relative numbers are small [27]. Their time of first appearance is not known, although it has been put at less than 4 weeks for SIV [32]. Persistence of viral production, even during sustained antiretroviral therapy, may be due to sources other than latently infected cells [30,33]. However, our results parallel the experimental evidence that PEP with antiretrovirals is effective only up to 72 h after intravaginal exposure of macaques to HIV2 [34]. They are also in accordance with policy that PEP commences within an hour [35] after sexual assault and that delays of a few hours are undesirable if an occupational encounter with a source patient is considered to be high-risk [31]. It may be concluded that after a needlestick penetration incident (or any suspected transfer of HIV) PEP should commence as soon as possible.

### 3.2. HIV transfer by heterosexual intercourse

The process of infection in a new host is complex when the transfer of virus particles is the result of sexual intercourse because there are uncertainties in the path the viruses take before they infect a target cell, see [5] for a discussion. For example, whereas it has been suggested that they enter through lesions in the new host, it has also been found that infectious virus particles may be harbored for up to 6 days in epithelial cells and cause infection [28].

Data have been collected for viral load and semen volume for vaginal sexual intercourse [7] and an empirical model for transmission described. It was found that infection by HIV-1 correlated with the burden of the virus in seminal fluid. Another study [29] found that the chances of transmission of the virus were much higher when the source individual was acutely infected and an empirical model was also proposed. We now incorporate into the model the dependence on depth of needle penetration [31], which would create further variability.

If the distribution of cases over state of source and type of needle were known, these results could be compared with data from CDC, Atlanta. Here, however, no distinction is made between high or low volume transfer or whether the source is acute or carrier. Of about 600000–800000 needlestick incidents per year in the USA, 2% involve HIV which results in about 10 infections. Thus, the overall probability of HIV infection due to a needlestick incident with an infected person is given as 0.003. The calculated probabilities seem compatible with these data.

In order to obtain some insight into the time-course of events, we use the formula for \( S_n(t) \) to obtain the probability that infection is at a time greater than \( t \). Due to uncertainty in the parameters we have done this for some extreme cases. The results are plotted in Fig. 2. The target-cell density \( T \) was always assumed to be 1000/mm\(^3\). The values of \( c \) employed were \( c = 2 \text{ day}^{-1} \) (left column) and the more recent estimate \( c = 23 \text{ day}^{-1} \) (right column) from [18]. The number of invading virus particles \( n \) was taken from the estimates for low and high volume cases, as indicated above. The minimum value of \( n \) must be 1 and the maximum number of virions transferred in the low volume case is about 100; the maximum number for high volume is about \( n = 1500 \). Two values of \( k \) were employed. The blue curves in Fig. 2 are for \( k = 6.5 \times 10^{-5} \text{ mm}^3/\text{day} \) and the red curves are for \( k = 2.7 \times 10^{-4} \text{ mm}^3/\text{day} \) [8,13].

From Fig. 2 it can be seen that the time interval during which infection may commence is extremely small when the largest number of virions is transferred, being only of the order of an hour or less. This is the case when the source of blood is from an acutely infected person. If the source person is not in an acute phase, then the time interval is much longer, being up to several hours or of order a few days if the viral clearance rate is low. It is of interest to try to relate these results to the time window for effective PEP [26], but this aspect is complicated by the role of latently infected cells, whose relative numbers are small [27]. Their time of first appearance is not known, although it has been put at less than 4 weeks for SIV [32]. Persistence of viral production, even during sustained antiretroviral therapy, may be due to sources other than latently infected cells [30,33]. However, our results parallel the experimental evidence that PEP with antiretrovirals is effective only up to 72 h after intravaginal exposure of macaques to HIV2 [34]. They are also in accordance with policy that PEP commences within an hour [35] after sexual assault and that delays of a few hours are undesirable if an occupational encounter with a source patient is considered to be high-risk [31]. It may be concluded that after a needlestick penetration incident (or any suspected transfer of HIV) PEP should commence as soon as possible.

### Table 1

<table>
<thead>
<tr>
<th>Final number</th>
<th>Initial number</th>
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<td>-</td>
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<td>21</td>
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### Table 2

<table>
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<td>0.00002–0.002</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.0004–0.99</td>
<td>0.0004–0.043</td>
<td></td>
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stochastic nature of the initial stages of infection, such as the probability that transferred virus particles gain access to target T-cells and the probability \( p_k \) that the viral population in the new host persists (does not go extinct). Thus, the probability of infection can be written

\[
P_{\text{inf}} = p_k(1 - \exp[-\gamma n]),
\]

where \( \gamma \) is to be determined. That is, uncertainties in the parameters \( c, k \) and \( T \) are absorbed into the single parameter \( \gamma \).

Now \( p_k \) has been estimated above as \( 1 - \exp[-R_0] = 0.997 \), which is so close to unity that we need only consider the first successful infection of a host cell by a virus. We may estimate \( \gamma \) approximately from the results in [7]. Accordingly, when \( n = 500 \) the probability of infection was between 0.0001 and 0.0003 and when \( n = 50000 \) the probability of infection was between 0.0039 and 0.0096. The values returned for \( \gamma \) are from 2 to \( 6 \times 10^{-4} \) and from \( 7.8 \times 10^{-8} \) to \( 1.9 \times 10^{-7} \), respectively. From these we choose a low value \( \gamma = 7.82 \times 10^{-8} \) and a high value \( \gamma = 6 \times 10^{-7} \). In Fig. 3 the probability of infection is plotted against the logarithm (to base 10) of the number of virions transferred for the low and high values of \( \gamma \). The range of values of \( n \) is divided into three parts from 1 to 100 (top), 100 to 10,000 (middle) and 10,000 to \( 10^6 \). For the lowest part of the range the probabilities of transmission are very small, not exceeding 0.00006. When the number of virions transferred is between 100 and 10,000 the values of \( P_{\text{inf}} \) are not greater than 0.006. For the highest part of the range (between \( 10^4 \) and \( 10^6 \)) the probabilities of infection are substantial, being of order 0.5 when \( n = 10^6 \) in the low \( \gamma \) case and when \( n = 10^7 \) for the high \( \gamma \) case.

### 3.2.1. Effectiveness of microbicides

In the last several years methods of precaution against HIV infection have been proposed including gels which may be applied by females before intercourse. To investigate theoretically the reduction in transmission probability which might occur when microbicides are employed, we suppose that if a microbicide has an efficacy of \( q \), then its (proper) application reduces the number of infectious virus particles transferred to the non-infected partner from \( n \) to \( (1 - q)n \). Thus, \( q = 1 \) implies a 100% effective microbicide. The determination of the percentage reduction in the probability of infection is calculated using the following formula:

\[
R_q = \frac{e^{-\gamma (1 - q)n} - e^{-\gamma n}}{1 - e^{-\gamma n}} \times 100\%
\]

which follows from the preceding expression. The results of these calculations, assuming an average value of the parameter \( \gamma = 8 \times 10^{-7} \), are shown in Fig. 4 for \( q \) from 0.2 to 0.7. The percentage reduction is close to \( q \) for small and intermediate numbers of virions transferred. However, for very large numbers of virions transferred, greater than about \( 10^5 \), the effectiveness of the microbicide is substantially less than \( q \) and in all cases becomes close to zero for viral transfers of order 10 million. Thus, microbicides may be able to prevent a new infection with small numbers of virions transferred but not when very large numbers of virions are transferred. This suggests that manufacturers of microbicides must investigate the dependence of efficacy on numbers of virions transferred.

### 4. Discussion

We have attempted to estimate with a simple stochastic model the probability that a new host becomes infected with HIV-1 after the physical transfer of a certain number of virus particles from an infected source person. The establishment of HIV-1 infection in a new host involves several stages, many of which are complex [5] and not completely understood nor easily quantified. We have considered both transfer by needlestick and transfer by male–female sexual intercourse. For the former we used data on blood volumes transferred and for the latter a comprehensive data set on measured viral loads in seminal fluid transferred [7].

For needlestick transmission the probability of HIV-1 infection in the most hazardous cases can be extremely high, (nearly unity) when the source is acutely infected and a large volume of blood is transferred. When low volume transfer occurs from a non-acute
source, the probability of infection may be negligible. Hence it is very important that health workers know in advance the HIV-1 status of patients whom they contact. Although we have not estimated the windows for effective PEP, it seems that as a general precaution, a person who falls prey to a needlestick injury should receive prophylactic treatment immediately.

For sexual transmission, the numbers of virions transferred and the parameters in the primary model have wide ranges of possible values which gives rise to very large ranges for the probability of infection per coital act. The probability may be as low as $4 \times 10^{-8}$ or as high as 1. The highest probability of infection occurs when the source person is in the acute stage and transfers a very large number of virus particles which themselves are highly infectious. The number and type of the new host receptors is also important [7] but we have absorbed its influence into the parameter $c$. We have found that microbicides may reduce the chance of infection, except when the number of virus particles transferred is greater than about $10^5$, which is not an infrequent occurrence [7]. Several factors have been mentioned in connection with the success or failure of microbicide gels to prevent infection, but the finding that increased rates of HIV infection occurred in clinical trials with cellulose sulphate gels has been disappointing and explanations are still being sought [36,37]. The simple modeling approach we have outlined for HIV could possibly also be applied to other viruses such as hepatitis C.

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