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"An Introduction to AIDS Modelling"

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These are preliminary lecture notes, intended only for distribution to participants.

Antigenic Diversity Thresholds and the Development of AIDS

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Longitudinal studies of patients infected with HIV-1 reveal a long and variable incubation period between infection and the development of AIDS. Data from a small number of infected patients show temporal changes in the number of genetically distinct strains of the virus throughout the incubation period, with a slow but steady rise in diversity during the progression to disease. A mathematical model of the dynamic interaction between viral diversity and the human immune system suggests the existence of an antigen diversity threshold, below which the immune system is able to regulate viral population growth but above which the virus population induces the collapse of the $CD4^+$ lymphocyte population. The model suggests that antigenic diversity is the cause, not a consequence, of immunodeficiency disease. The model is compared with available data, and is used to assess how the timing of the application of chemotherapy or immunotherapy influences the rate of progress to disease.

MUCH UNCERTAINTY STILL SURROUNDS THE PROCESSES governing the development of acquired immunodeficiency syndrome (AIDS), after an individual is infected with the human immunodeficiency viruses (HIV-1 and HIV-2). There is a long and highly variable incubation period for AIDS, with roughly 50 percent of male homosexuals developing the disease within 10 years after infection (*1*), and a slow but steady depletion of $CD4^+$ T-helper or inducer lymphocytes over this period in those who develop AIDS (*2*). The interaction between the viral population and the host's immune and other systems is very complex, with the virus being able to infect not only cells within the immune system but also a wide variety of other cell types in the brain, the gastrointestinal tract, the kidney, and other tissues (*3*).

Various explanations have been offered for the slow impairment of immune functions and the increased susceptibility of AIDS patients to opportunistic infections. These range from those based on the ability of the virus to kill $CD4^+$ cells, to those that invoke the presence of other infectious agents, such as mycoplasms, as necessary cofactors for the development of disease (*4*).

Understanding what is going on might seem to have been made more difficult by the discovery of great genetic diversity in viral isolates obtained either sequentially from the same infected individual or from different individuals (*5*). As a retrovirus, HIV lacks mechanisms that correct errors during replication, and the result is an error rate of about 10^{-4} per base, or one misincorporation per genome per replication cycle (*6*). Thus, each viral genome must be viewed as being different from any other, and viral isolates must be

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thought of as populations of closely related genomes. Such ensembles of genomes are called quasispecies (7). The different mutants within such a quasispecies may exhibit marked differences with respect to biological properties such as cell tropisms, cytopathic properties, replication rates, and surface antigen characteristics (notably, for HIV, those associated with the V3 hypervariable region of the viral envelope protein gp120) (8). This antigenic variability is particularly significant in helping a viral quasispecies to persist under immunological attack; many infectious agents [and, in particular, many lentivirus infections (9)] exhibit the ability to vary their dominant surface antigens, often by mutation events in replication, which helps them escape surveillance and destruction by the host's immune system (10).

We propose that the genetic variability of HIV is not so much a complication, as the key to understanding the development of AIDS. In particular, we examine a mathematical model for viral multiplication that explicitly describes the interplay between the total diversity of viral strains (which in general will increase over time) and the suppressing capacity of the immune system. The model shows that the human immune system is only able to mount an effective response against HIV quasispecies whose diversity is below some threshold value; once the population of viral strains exceeds this "diversity threshold" the immune system is no longer able to regulate viral replication, with consequent destruction of $CD4^+$ cells.

These ideas are used to interpret new data from longitudinal studies of two infected patients (11). The model also helps explain many puzzling aspects of infection and the development of disease, including the variable likelihood of transmission between infected and susceptible sexual partners or infected mothers and unborn infants, the variety of cell types that the virus appears able to infect, the variable duration of the incubation period of AIDS, and the great diversity of symptoms of disease exhibited by patients. Moreover, if the ideas encapsulated in the model are basically correct, they have implications for the way different treatments (chemotherapy or immunotherapy) may alter the dynamic interplay between viral diversity and immune suppression, and thence the rate of development of AIDS.

Genetic Change in Viral Populations During the Incubation Period of AIDS

For a short but variable period—a few weeks to a few months—after an individual is infected with HIV-1, virus is typically found in the blood (viremia), and high levels of virus replication can be observed. Antibodies then appear in blood serum (seroconversion), after which it becomes difficult to isolate the virus; viral antigens are often undetectable during the long but variable asymptomatic or incubation period between primary HIV-1 infection and the occurrence of AIDS. This incubation period is characterized by low viral replication (interspersed with minor and short-lived upsurges of viremia in some patients), and by constant or slowly decreasing numbers of $CD4^+$ cells. As AIDS develops, viral isolation becomes easier; the proportion of infected cells in peripheral blood is 100 to 1000 times higher in AIDS patients than in asymptomatic individuals (12). In AIDS patients, viremia can be reduced, and $CD4^+$ cell counts raised, by treatment with Zidovudine (AZT), but such changes may be transient, only lasting 6 to 12 months (13).

These temporal trends in virus antigen (P24) and $CD4^+$ cell counts were observed in two homosexual men in Amsterdam who seroconverted in 1985 (14). One individual developed AIDS 55 months after becoming infected with HIV-1 (specifically, from the first p24 antigenemia peak), and chemotherapy was begun in late 1989 (Fig. 1A). The second individual remained asymptomatic (Fig. 1C). Infected individuals appear to harbor a quasispecies of the virus, with a broad distribution of molecular sequences. Sequence variation is not uniform over the viral genome; the *gag* and *pol* genes, for example, show less variability than the *env* gene. Within the *env* gene, there are five hypervariable regions, V1 to V5. The immunodominant V3 loop is a region of about 30 amino acids within the envelope protein gp120; the V3 region contains an epitope that elicits isolate-specific neutralizing antibodies. This V3 region exhibits high mutation rates, and the change of one amino acid in this V3 region can restrict recognition by neutralizing antibodies (15).

Some evidence indicates that the biological properties of HIV-1

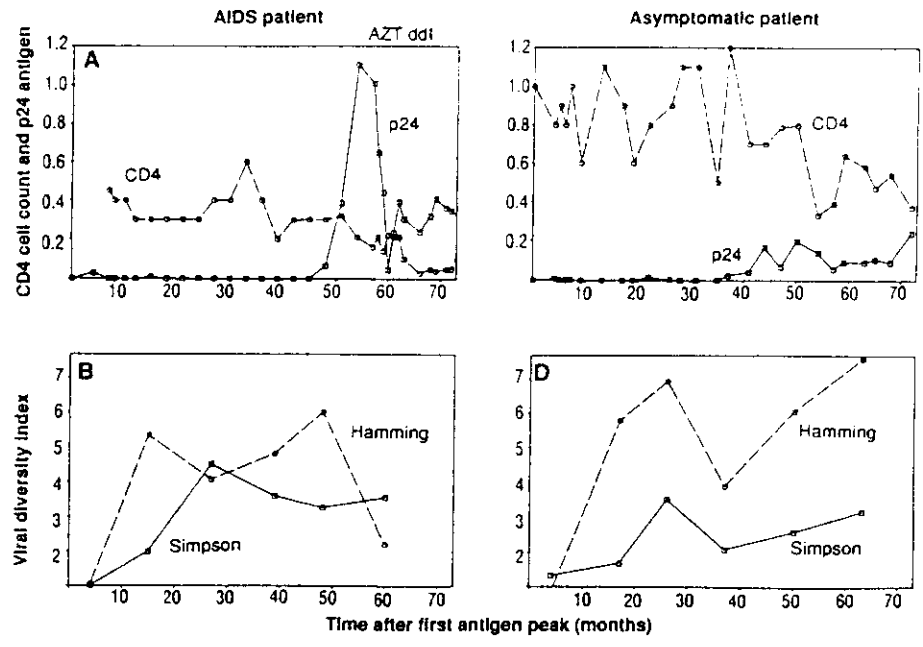

Fig. 1. (**A** and **C**) $CD4^+$ cell counts ($\times 10^9$ per liter) and p24 antigen ($\times$ 2000 pg/ml) for two homosexual male patients, 1 and 495 (14). For both men, the first serum sample was taken in 1985 at the moment of p24 antigen conversion, 0.5 to 3 months before the development of antibodies to HIV. Successive samples were obtained 13, 22, 34, 46, and 59 months later for patient 1, and 12, 24, 36, 45, and 57 months later for patient 495. Patient 1 remained asymptomatic during follow-up (only nonsyncytium-inducing (NSI) viruses could be isolated) and received no anti-viral therapy. Patient 495 developed AIDS (CDC-IV C1) 55 months after antigen conversion, began AZT treatment in month 56, and was switched to ddI treatment in month 64 (a change from NSI to SI viruses was observed between 1988 and 1989). (**B** and **D**) The genetic diversity of the V3 loop of the envelope protein gp120 was extremely low at time of seroconversion (11 of 11 sequences identical for the V3 loop from patient 495, and 6 of 7 sequences identical from patient 1), and increased during the asymptomatic period. Nucleotide sequences of a region containing the V3 loop were obtained by repeated isolation of virus particles from the serum, transcription of the viral RNA into cDNA, and double PCR (polymer chain reaction) amplification (32). From 8 to 12 sequences were analyzed at six time points. The viral population diversities for both patient 1 (D) and patient 495 (B) were calculated from the amino acid sequences by two different methods: the mean Hamming distance (21) for the entire sequence of 93 amino acids and the Simpson index (as defined in the text), for only the 36 amino acids in the V3 loop.

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may vary significantly from clone to clone (*16*). There is, for example, measurable variation among the replication rates of HIV-1 strains in CD4$^+$ cells (*17*). In general, more virulent strains tend to appear later in the incubation period (with virulence defined in terms of cytophatic properties and high replication rates) (*3, 18*). Thus HIV-1 isolates from asymptomatic carriers tend to grow slowly and to have low titers of reverse transcriptase (RTase) activity, whereas isolates from patients with "AIDS related complex" (ARC) or with AIDS grow rapidly, induce cell syncytia more frequently, and show high RTase activity (*18*). Mathematical models of the interaction of HIV-1 and CD4$^+$ suggest that evolutionary forces may drive selection for more virulent strains (*19*).

To assess how genetic variation within the HIV quasispecies infecting a given patient changes over time, we studied viral isolates from serum samples taken at intervals of 10 to 12 months from the two homosexual males referred to above (Fig. 1, A and C). Variation in the V3 domain was examined by cloning sequences derived from the virus's genomic RNA, which had been isolated from serum, amplified by the polymerase chain reaction (PCR), treated with RTase, and cloned into PGem. The first serum sample was taken during the first peak in p24 antigenemia. An appropriate inverse measure of the quasispecies diversity is given by the ecologists' Simpson index, $D = \Sigma_i (\nu_i/\nu)^2$, where ν_i denotes the number of type i sequences in the sample, and ν denotes the total number of sequences; the index takes into account the frequency of sequence i in relation to the total sample of sequences. For the two patients described earlier, we plotted the parameter $1/D$ and the mean Hamming distance (*20*) for each sample as a function of time (Fig. 1, B and D). In both patients the genetic diversity was extremely low at the time of seroconversion and it increased during the asymptomatic period. In the patient who developed AIDS, diversity reached a peak before the onset of AIDS and seemed to decline thereafter (Fig. 1B). The pattern of decline in diversity as AIDS develops may appear counterintuitive. The observed pattern was, however, what would be expected from sampling theory (which underlies the definition of the Simpson's index) when isolates are drawn from a large population of different mutants during the AIDS phase; in this phase, which is characterized by relatively unregulated growth of the viral population, strains with faster replication rates will be most abundant and will be most likely to be detected (*21*). The apparent decline in diversity is thus caused by selection for fast replicating mutants once the immune system can no longer regulate the viral population (*22*).

The observations that the number of different strains increases over time (provided that sampling biases are taken into account), and that virulent strains occur more frequently once symptoms of disease develop, lead us to ask whether this pattern is a cause, or a consequence, of immunodeficiency. To pose this question more sharply, we used a simple mathematical model of how the evolutionary dynamics of HIV-1 quasispecies interact with the immune system.

Mathematical Model of Virus Evolution During the Course of This Infection

The model, an extension of an earlier one (*23*), keeps track of the changes, over time, in the densities of the populations of the various viral strains and different kinds of CD4$^+$ cells. The model consists of a system of ordinary differential equations, whose structure reflects what we hypothesize are three key features distinctive to HIV infections. (i) The continuing appearance of new antigenic variants, or "escape mutants," of the virus enables the overall virus population to evade elimination by the immune system. (ii) Immunological responses directed against the virus involve a specific response to individual strains (subpopulations of CD4$^+$ cells specifically directed toward immunological attack against that strain) along with a cross-reactive response that acts against all strains. (iii) Each viral strain can infect and subsequently kill all CD4$^+$ cells, regardless of their specificity to a particular mutant. More precisely, the assumption (ii) deals with subpopulations of CD4$^+$ cells that can mount immunological attack against specific viral epitopes; if an epitope is conserved among mutants then the resulting immune response is cross-reactive, but if it is within a hypervariable region (such as the V3 loop) then only some viral variants are recognized by this particular response.

The model resulting from these assumptions has four kinds of

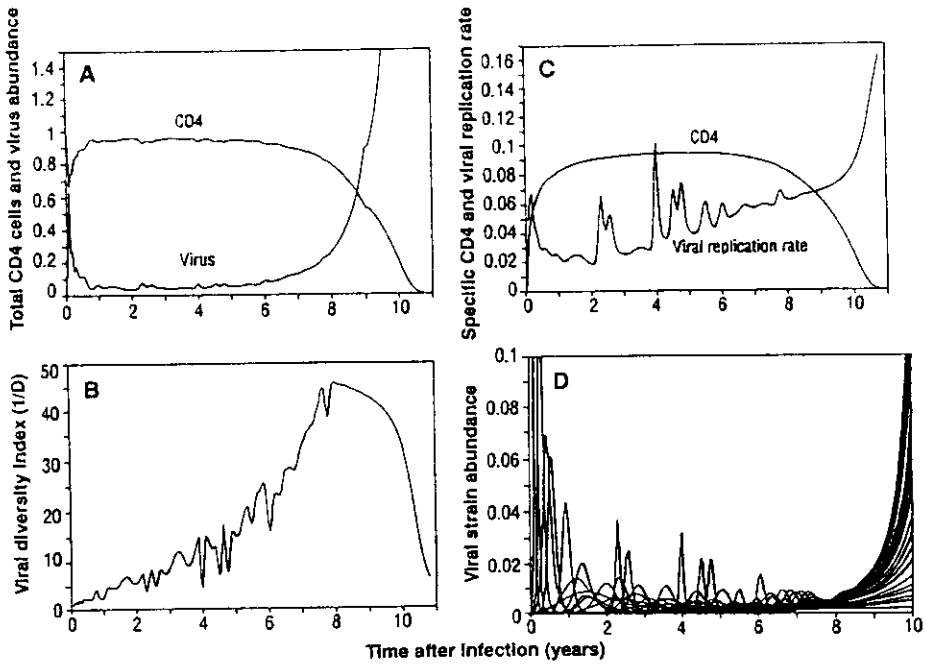

Fig. 2. A computer simulation of changes over time in HIV abundance and CD4$^+$ cell counts in an individual patient, as described by Eqs. 1 to 4. (**A**) Total virus and CD4$^+$ cell abundance in arbitrary units. (**B**) Antigenic diversity of the virus population measured by the Simpson index, D; the plot shows $1/D$ as a function of time. (**C**) The average virus replication rate $r = \Sigma r_i \nu_i/\nu$ "switches" from low to high as AIDS develops (the unit of the replicative rate is yr^{-1}); superimposed is the total density of CD4$^+$ cells (arbitrary units) directed to HIV antigens. (**D**) Abundance of 40 different HIV variants (arbitrary units) that evolve during the course of infection. The parameter values in Eqs. 1 to 4 are taken to be: $K = 100$; $d = 1$; $k = k' = 0.1$; $u = 1$; $r_i' = 3\ r_i$; $s_i = 9.5\ r_i$; $p_i = 20\ r_i$ (all rates have dimension yr^{-1}). The variable r_i was taken from an exponential distribution, with mean 0.05. This implies that the diversity threshold is $n_c = 25$.

variables: v_i, y, x_i, and z, which denote the densities of virus strain i, total CD4$^+$ cells, CD4$^+$ cells specific to strain i, and CD4$^+$ cells that mount cross-reactive responses to all strains, respectively. The total virus population is represented by $v = \Sigma v_i$. The rates of change of each variable with respect to time ($t = 0$ being the point when the host acquires infection) are then:

$$\text{Virus population } dv_i/dt = f_i(v_i,y) - v_i(s_iz + p_ix_i)\ i = 1, 2, \ldots, n \quad (1)$$

$$\text{Total CD4}^+ \text{ cells } dy/dt = K - dy - uvy \quad (2)$$

$$\text{Strain-specific CD4}^+ \text{ cells } dx_i/dt = kv_iy - uvx_i\ i = 1, 2, \ldots, n \quad (3)$$

$$\text{Cross-reactive CD4}^+ \text{ cells } dz/dt = k'vy - uvz \quad (4)$$

The variables x_i and z are some fraction of the total CD4$^+$ cell population. In Eq. 1 the term $f_i(v_i,y)$ denotes the reproductive rate of viral strain i. We define this function as $f_i(v_i,y) = (r_i' + r_iy)v_i$ to denote replication of strain i at a per capita rate r_iy, arising from infection of CD4$^+$ cells (y), along with a low but constant background replication rate r_i' to denote replication of the virus in cells other than of the CD4$^+$ type (such as macrophages or monocytes). The term s_izv_i represents the killing of the strain i by cross-reactive CD4$^+$ cells, and the term $p_ix_iv_i$ denotes the killing by strain-specific CD4$^+$ cells. In Eq. 2, K is the recruitment rate of CD4$^+$ cells (from the thymus), d is the per capita death rate, and uvy denotes the rate at which cells are killed by any member of the total virus population. Equivalently, the recruitment terms in Eqs. 3 and 4 (kv_iy and $k'vy$, respectively) denote activated cells joining the strain-specific and cross-reactive CD4$^+$ cell populations. Activated strain-specific and cross-reactive lymphocytes are killed by the virus at net rates uvx_i and uvz, respectively, in Eqs. 3 and 4. The total number of virus strains, n, is not constant, because replication errors generate new mutants that escape the current strain-specific immune responses and persist in the presence of the cross-reactive responses. This introduces a stochastic element, where the probability that a new strain is generated in the time interval between t and $t + dt$ is given by $Pv(t)dt$. The constant P convolves the replication rate of the virus population and the probability that mutation generates a new strain that is not recognized by the current strain-specific responses.

The main properties of the above model can be understood from analytic and numerical studies of the set of equations. One such simulation is presented in Fig. 2. Initially we see high levels of viremia (characteristic of primary HIV infection), but the immune response soon suppresses the strains of the infecting inoculum and of early mutants (Fig. 2A). However, over time there arise new mutants that are not recognized by the current strain-specific immune responses (escape mutants), and these mutants generate mini-outbreaks of viremia (Fig. 2, A and D). These mini-outbreaks are in turn suppressed by a combination of specific and cross-reactive responses. As the total number of antigenically distinct viral strains increases over time (Fig. 2B), the total population of CD4$^+$ cells begins to decline (*24*) (Fig. 2A). After a long period of low viremia (with sporadic small blips), viral abundance begins to rise rapidly and, concomitantly, CD4$^+$ cell abundance declines to low levels. This final phase represents the collapse of the immune system and the development of AIDS. Over this long period, the average replication rate of specific CD4$^+$ cells initially rises, attains a plateau, and then declines as the total virus population escapes regulation by the immune system (Fig. 2C). Viral diversity, as measured by the inverse of the Simpson's index, initially increases, but in the later stages declines as the faster replicating strains predominate (even though the total number of strains continues to increase) once immunological regulation breaks down (Fig. 3). The patterns generated by the model are quite similar to those observed in infected patients (compare Figs. 1 and 2).

Insight into the nonlinear mechanisms that generate the slow development of immunodeficiency and the final rise in viral population abundance can be gained from analytic investigations of a simplified version of the above equations (*23*). Specifically, assume that all viral strains have the same replication rate, r (regardless of the total density of CD4$^+$ cells), and that the parameters s and p in Eqs. 1 to 4 are also constant and independent of strain type. With these assumptions, we can see that the total abundances of specific and unspecific CD4$^+$ cells converge quickly, as infection progresses, to steady levels x and z, respectively. Equation 1, describing how the density of viral strain i changes over time, now becomes $dv_i/dt = v_i(r - sz - px_i)$. In the parameter region where the strain replication rate, r, can outrun the unspecific immune response, but not the combined effects of unspecific and specific responses (that is, when $px > r - sz > 0$), only the continuous generation of new escape

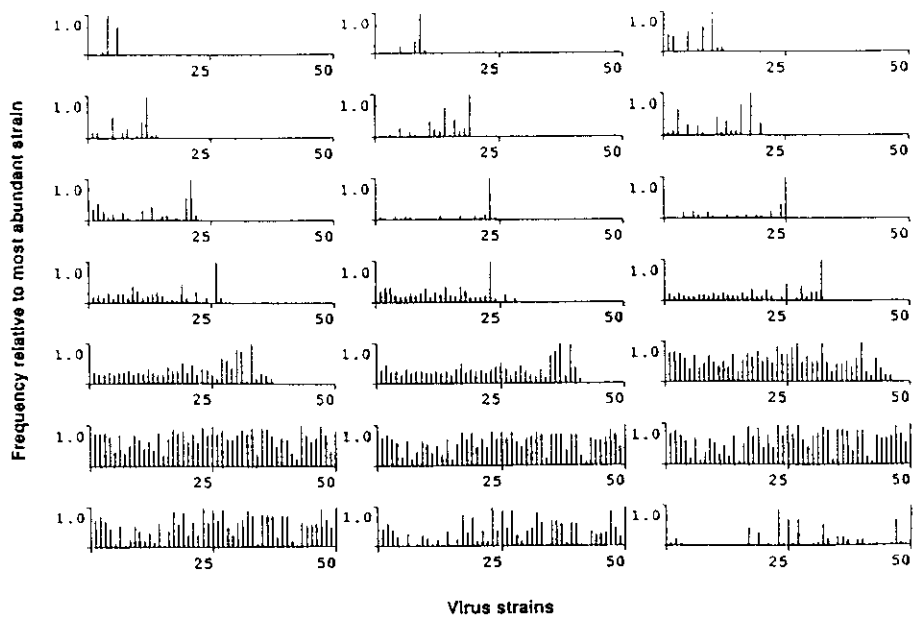

Fig. 3. Diversity plot for the simulation shown in Fig. 2. Viral diversity is sampled every 0.5 year (starting from the top left line). Each graph shows the different strains (labeled 1-50 on the x axis) and their abundance relative to the predominant strain (on the y axis). This figure illustrates the fluctuating, nonmonotonic increase in viral antigenic diversity. The number of different strains increases continuously, but the diversity of the population (as measured by the Simpson index) does not (Fig. 2B).

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mutants enables the virus population to persist under immunological attack. The immune system should then be able to control the strain labeled i if dv_i/dt is eventually negative, that is if $r - sz - px_i < 0$. The immune system can therefore control the total viral population only if this inequality holds for all n values of i, where n is the total number of strains. This implies the restriction that (*23*)

$$n < n_c = px/(r - sz) \quad (5)$$

Thus, the total virus population can only be regulated by the immune system provided that the number of antigenically distinct strains present, n, is less than a critical antigenic diversity threshold, n_c. A generalized version of the threshold criterion, Eq. 5, can be derived when each escape mutant has a different value for the biological parameters r_i, s_i, u_i, p_i, and k_i in the modified Eqs. 1 to 4 (*25*). This threshold criterion is a peculiarly nonlinear property of a system in which the virus can kill any of the cells that are directing the immunological attack against it, but in which different viral strains require specific immune responses for effective control.

In short, as antigenic diversity increases over the course of HIV-1 infection (as new mutants accumulate), the diversity itself enables the virus population to escape control by the immune system and, concomitantly, results eventually in the destruction of this system. More specifically, the virus population can be seen to escape regulation once the inverse of the Simpson's diversity index, $1/D$, exceeds the value of the antigenic diversity threshold, n_c. The theory therefore provides an explanation of the slow progression of HIV infection to AIDS based on the slow accumulation of immunologically distinct HIV strains via the generation of escape mutants (over the asymptomatic stage); it ends with the breaching of the diversity threshold, upon which the virus population escapes regulation and induces the destruction of the immune system.

The model provides other insights. For example, the generation of escape mutants by replication errors is a chance process. Hence it can happen that, in some of the simulations with a given set of parameters, the infection is cleared from the host (viral abundance is reduced effectively to zero). More generally, the average infected individual develops AIDS only if each virus strain produces at least one new escape mutant before being suppressed by the immune system; the average number of escape mutants is measured by R_0, the basic reproductive number (*26*). The prediction that the viral population may sometimes be eliminated during the asymptomatic phase of infection is of interest in that some infected individuals (both adults and infants born to infected mothers) remain antibody positive but convert to a state where antigen is undetectable (*27*). It could be that some fraction of seropositive individuals have been able to clear the viral infection because of chance effects in the timing of the appearance of new strains.

Another prediction deals with temporal patterns in the diversity of fast replicating strains in the viral population. Once the diversity threshold is exceeded, strains with faster replication rates would predominate in the rapidly growing viral population, although slower growing strains would also expand their population sizes. The model therefore suggests that the increased frequencies of fast-replicating strains observed in patients with symptoms of disease is a consequence of the antigenic diversity threshold being exceeded, and not the cause of the severe immunodeficiency (Fig. 2C). Also Eq. 5 has the implication that a "weaker" immune system (smaller x or z) implies a lower diversity threshold, and hence faster progression to AIDS in infants and, to a lesser extent, in older people; this is in accord with the facts.

The qualitative agreement between a range of predictions and the patterns observed in infected patients engenders confidence in the biological assumptions crudely captured by the model and prompts us to use this template to assess (i) the potential impact of immunotherapy and chemotherapy in delaying the onset of disease and (ii) the problems in vaccine development.

Vaccination and Immunotherapy

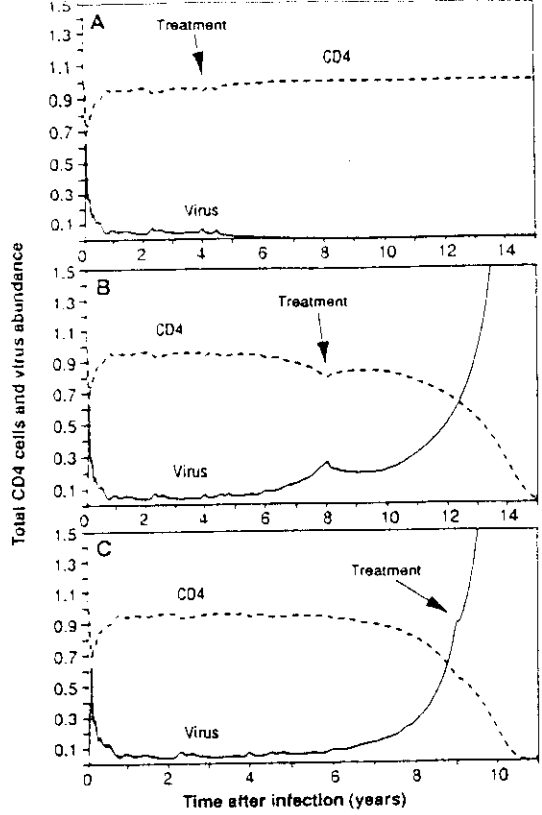
How many of the large number of different antigenic strains of HIV-1 must be recognized by a vaccine if it is to prevent the progression from infection to AIDS? To address this question, we consider a simple branching process that caricatures the emergence and loss of escape mutants (*28*). This leads to an expression for the probability, μ, that infection with a single strain of HIV-1 will eventually lead to AIDS (that is, to the number of strains, n, exceeding the diversity threshold, n_c); this expression for μ involves only the single parameter R_0 defined as the average number of escape mutants produced by each strain. A successful vaccine must reduce R_0 below unity. If R_0 is originally large, it will be difficult for a vaccine that stimulates strain-specific immunity to bring it below unity. Alternatively a vaccine could stimulate the production of cross-reactive $CD4^+$ cells (to increase the magnitude of z in Eq. 1), which could suppress the virus if its replication rate is unable to outrun the unspecific immune response ($f_i < s_i v_i z$ for all i in Eq. 1).

Similar principles apply to immunotherapy, which aims to enhance the specific *or* non-specific responses in patients who are already infected. The success of an immunogen that can neutralize, say, 80 percent of all possible HIV variants, depends on the magnitude of R_0. If $R_0 = 10$, then an 80 percent reduction in its magnitude decreases the probability of developing AIDS from 0.9999 to 0.8; but if $R_0 = 20$, then an 80 percent immunogen decreases the chances from essentially unity to only 0.98, which is still rather poor (*28*). As yet we have little idea for the magnitude of R_0 for HIV-1.

Another relevant question is how the rate of progression to AIDS is affected by when immunotherapy starts. We have explored the dynamical behavior of Eqs. 1 to 4 when immunotherapy is begun at a defined time, t, from the point of infection and continues thereafter (the basic parameter values are as in Fig. 2). Figure 4, A to C, shows the simulated system with immunotherapy begun 4, 8, and 9 years, respectively, after the initial infection. The immunogen used in the treatment was assumed to stimulate immunological recognition of 80 percent of all strains present, and to enhance the strain-specific response to these variants by a factor 5 (in Eq. 3, $k = 5$ for 80 percent of the strains, and $k = 1$ for 20 percent of the strains). When treatment was started at year 9, it had essentially no effect; when started in year 8, it prolonged the incubation period of AIDS by roughly 3 years; and when treatment started in year 4, viral abundance was still low 15 years after the original infection. Thus, Eqs. 1 to 4 suggest that much may be gained by treatment early in the course of infection. This conclusion is, however, tentative, given the many uncertainties about how potential therapies may stimulate the immune system.

Chemotherapy and Drug-Resistant Strains of the Virus

A number of studies, both in vivo and in vitro, have demonstrated the ability of HIV-1 to evolve resistance to the drug AZT (*29*). Indeed, the observation that AZT suppresses viremia in AIDS patients only for periods of roughly 6 to 12 months is probably associated with the emergence of resistant strains, a finding that raises several questions. For example, does the timing of chemotherapy affect the speed at which resistant strains emerge; and does



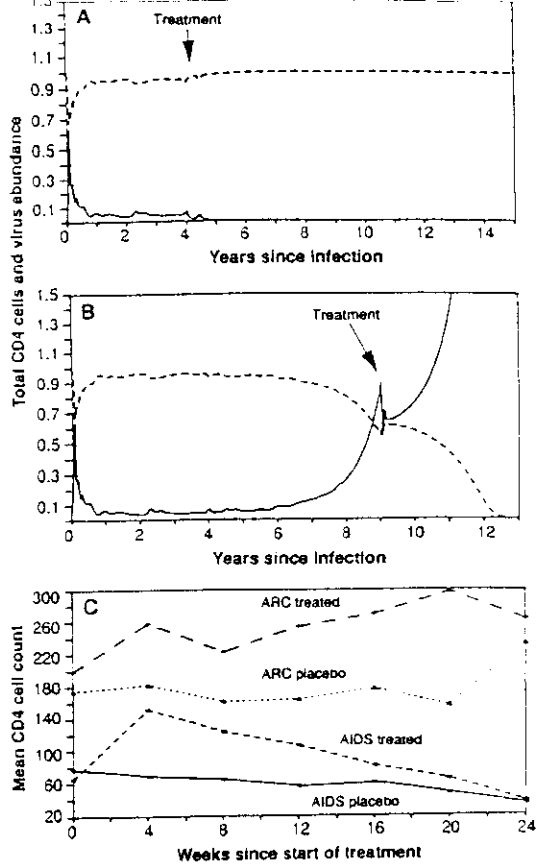


Fig. 4 (left). Simulation, with immunotherapy starting at different time points after infection. (**A**) At 4 years; (**B**) at 8 years, (**C**) at 9 years. The immunogen increases the strain-specific response to 80 percent of all viral variants (that is, $k = 5$ for recognized strains and $k = 1$ for nonrecognized strains). This simulation suggests that early treatment is more effective because the virus diversity is lower then. The parameter values are as defined in Fig. 2. Virus abundance and CD4 cell count in arbitrary units. **Fig. 5 (right).** Chemotherapy (for example, AZT treatment) may reduce the viral replication rate. In these simulations chemotherapy is started (**A**) 4 years and (**B**) 9 years after infection; once begun, chemotherapy is applied continuously throughout the duration of the simulation. This leads to an increase in the disease-free period, which is more pronounced if treatment begins earlier [compare (A) and (B)]. The evolution of drug-resistant strains is modeled by the assumption that 20 percent of all HIV strains are less sensitive to the drug. Treatment reduced the replication rates of AZT-sensitive strains to one-tenth of their original value; replication rates of AZT-resistant strains remained unchanged. All other parameter values are as defined in Fig. 2. Virus abundance and CD4 cell count are given in arbitrary units. (**C**) Data for the population dynamics of $CD4^+$ cells ($\times 10^6$ per liter) in ARC and AIDS patients under AZT treatment (*13*); initially the $CD4^+$ cell count increases, but it decreases as resistant strains are selected. The observed dynamics are similar to those recorded in the simulations.

treatment with AZT in the asymptomatic phase of infection significantly delay the onset of symptoms of disease? Equations 1 to 4 can be used to reflect the impact of chemotherapy, thus indicating answers to these questions.

In Fig. 5 an example is presented that records numerical simulations in which the drug dose acts to reduce the replication rate of 80 percent of the strains by a factor of 10, while the remaining 20 percent of strains are drug resistant (having the same replication rate as before treatment, as in Fig. 2). In the first simulation treatment was started at year 4, and in the second at year 9, from the onset of infection. The principles that emerge are similar to those for simulated immunotherapy. Treatment late in the course of infection has modest impact (delaying rapid viral population growth by about 1 to 1.5 years in this example), whereas early treatment can significantly lengthen the incubation period. The patterns of change in viremia and $CD4^+$ cell abundance are similar to those observed in treated patients (Fig. 5C).

Future Directions

The ideas presented here (and summarized by Eqs. 1 to 4) suggest that viral antigenic diversity is the cause, not a consequence, of the development of AIDS. The theory rests on three main assumptions, each supported by data. (i) Replication errors produce antigenically distinct strains of HIV-1 at a high rate; (ii) among these strains are "escape mutants," whose control requires additional strain-specific immune responses; and (iii) all strains of the viral quasispecies can kill any of the $CD4^+$ cells that orchestrate both specific and unspecific immunological responses. The nonlinear dynamics of this peculiar system of interacting population of cell types can generate an antigenic diversity threshold: the immune system is able to regulate a viral population whose diversity is below a threshold value, but is unable to constrain growth once diversity becomes too high. Thus, for this particular system, the action of strain-specific immunity in creating antigenic diversity paradoxically ends up triggering the destruction of the immune system itself.

The mathematical model leads to clearly testable (and falsifiable) hypotheses, which survive comparison with the admittedly limited data that are available from longitudinal studies of patients over the incubation period of AIDS. These observations include a two-peaked pattern of viral abundance (with peaks during the initial HIV infection, and as ARC and AIDS develop), small sporadic upsurges in the intervening asymptomatic phase, the coexistence of an increasing number of antigenically distinct viral strains over the incubation period, and the dominance of fast replicating strains in ARC or AIDS patients (with the last 2 features resulting in a "humped" pattern of viral diversity, as measured by Simpson's index or other such measures). The model also makes testable predictions about control strategies, including the suggestion (subject to the caveats above) that immunotherapy and chemotherapy are likely to be more effective in delaying the onset of symptoms if they are begun early in the course of the infection.

The model contains parameters whose values must be assigned.

Although predicted patterns are in qualitative agreement with observed trends, the quantitative details depend on the precise values of the parameters. Accurate information about these basic parameters is lacking, because the population biology of cell infection and death, of viral population growth rates, or of the rate of production of "escape mutants" during replication require further studies and, if possible, studies in vivo (*30*).

In general, we need more studies of the population biology of the human immune system and its interaction with infectious agents. The population dynamics of such systems are typically highly nonlinear, so that changes in cell populations over time cannot be inferred simply from descriptions of the interactions between different types of individual cells and viral variants, no matter how detailed these may be (*19, 31*). Our model of antigenic change in HIV-1 infection shows that a mathematical description of the biological processes can help us interpret observed trends and define what needs to be measured (*33*).

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$$\sum_{i=1}^{n} (r_i - s_i z)\, u_i/p_i k_i > 1$$

(M. A. Nowak, in preparation). A few strains with very high reproductive rates, or high pathogenicity in CD4$^+$ cells, can now have disproportionate influence on whether the diversity threshold is breached.
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Drugs, sex and HIV: a mathematical model for New York City

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CONTENTS

SUMMARY

A data-based mathematical model was formulated to assess the epidemiological consequences of heterosexual, intravenous drug use (IVDU) and perinatal transmission in New York City (NYC). The model was analysed to clarify the relationship between heterosexual and IVDU transmission and to provide qualitative and quantitative insights into the HIV epidemic in NYC. The results demonstrated the significance of the dynamic interaction of heterosexual and IVDU transmission. Scenario analysis of the model was used to suggest a new explanation for the stabilization of the seroprevalence level that has been observed in the NYC IVDU community; the proposed explanation does not rely upon any IVDU or sexual behavioural changes. Gender-specific risks of heterosexual transmission in IVDUs were also explored by scenario analysis. The results showed that the effect of the heterosexual transmission risk factor on increasing the risk of HIV infection depends upon the level of IVDU. The model was used to predict future numbers of adult and pediatric AIDS cases; a sensitivity analysis of the model showed that the confidence intervals on these prediction estimates were extremely wide. This prediction variability was due to the uncertainty in estimating the values of the models' thirty variables (twenty biological-behavioural transmission parameters and the initial sizes of ten subgroups). However, the sensitivity analysis revealed that only a few key variables were significant in contributing to the AIDS case prediction variability; partial rank correlation coefficients were calculated and used to identify and to rank the importance of these key variables. The results suggest that long-term precise estimates of the future number of AIDS cases will only be possible once the values of these key variables have been evaluated accurately.

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1. INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a major public health problem in New York City (NYC); as of September 1990 over 28000 adult AIDS cases and approximately 700 pediatric AIDS cases have been reported from the City (NYC Health Department 1990). Intravenous drug users (IVDUs) have become a significant risk group for the human immunodeficiency virus (HIV); IVDUs can acquire the virus through either heterosexual transmission or through IVDU (by the sharing of needles or other injecting equipment) (Curran *et al.* 1988; des Jarlais *et al.* 1989; Friedland & Klein 1987; Moss 1987). Seropositive IVDUs can heterosexually transmit HIV to their non-IVDU sex partners, and seropositive female IVDUs are the primary source for perinatal transmission in NYC (Curran *et al.* 1988; des Jarlais *et al.* 1989; Friedland & Klein 1987; Moss 1987). Consequently, IVDUs now play a major role in HIV transmission and disease in NYC. Furthermore, as it has been estimated that there are approximately 200000 addicts in the NYC IVDU community (Frank *et al.* 1978), large numbers of AIDS cases that are attributable to IVDU, heterosexual or perinatal transmission may be expected in the future.

Mathematical models may be conceptualized as thought experiments, and therefore models are useful when physical experiments are impossible to perform because of time, monetary or ethical constraints. As with physical experiments, the behaviour of the system is understood by altering the assumptions or parameter values and measuring the effect on the outcome variable. Thought experiments should be designed in the same manner as physical experiments, with only a few variables; the specific variables should be determined by the particular research objectives. In this study, only the epidemic of HIV that is due to IVDU, heterosexual and perinatal transmission is modelled, the effects of homosexual and bisexual transmission are excluded. Mathematical models may be used to make quantitative predictions; for example, models may be used to estimate the future number of AIDS cases. However, the precision of these predictions is often limited by the uncertainty in estimating both the sizes of the risk groups and the values of the biological-behavioural transmission parameters (Anderson & May 1988). Models may also be used to make qualitative predictions; for example, models may be used to explicate the mechanism that links specific risk behaviours of individuals with the seroprevalence level of a population. In this study, we formulate and analyse a model in order to generate both qualitative and quantitative predictions.

In this paper we present a data-based mathematical model that we have formulated and analysed to assess the epidemiological consequences of heterosexual, IVDU and perinatal HIV transmission. The model was designed to reflect the specific transmission dynamics of these three processes in New York City. It was used in two ways to understand HIV/AIDS epidemiology. First, the model was used to suggest a new explanation for the observed IVDU seroprevalence pattern in NYC and to explore the effect of the heterosexual transmission risk factor on increasing the risk of HIV infection in IVDUs. Second, the model was used to predict future numbers of adult and pediatric AIDS cases, to assess the variability in these predictions and to identify the key variables that contributed to this prediction imprecision. This paper is organized in the following manner: the model structure is described and justified, the model equations are presented, the qualitative behaviour of the model is explored through a specific scenario analysis, and finally the quantitative behaviour of the model is investigated by a sensitivity analysis.

2. JUSTIFICATION OF MODEL STRUCTURE

(*a*) *Basic structure*

The majority of IVDUs in NYC are heroin users (Hubbard *et al.* 1984; Joseph *et al.* 1981), many of whom became addicts in the late 1960s and the early 1970s when there was an increased availability of heroin (des Jarlais & Uppal 1980). Hence, the mathematical model presented in this paper is formulated for a fixed cohort of IVDUs; three transmission routes are modelled: IVDU (by sharing needles or other IVDU equipment), heterosexual and perinatal. IVDU behaviour and sexual behaviour are extremely heterogeneous and significant gender differences are found for these two types of behaviours (Chaisson *et al.* 1989; Coleman & Curtis 1988; des Jarlais & Friedman 1988*a*, *b*; des Jarlais *et al.* 1988*a*, *b*; Friedland *et al.* 1985; Schoenbaum *et al.* 1989, 1990); therefore, the model includes gender-specific behavioural heterogeneity.

Two predominant patterns of needle-sharing behaviour have been identified in NYC. IVDUs have been found to share needles and other IVDU equipment with either strangers in shooting galleries or with close friends and relatives in other social environments (des Jarlais *et al.* 1986*a*, *b*; Schoenbaum *et al.* 1989); these two types of IVDUs may be called stranger-users or buddy-users, respectively. Although both types of IVDUs share needles, they have significantly different risks of acquiring HIV. The risk of HIV infection in stranger-users depends upon the rate of sharing needles, the HIV transmission efficiency per injection and the seroprevalence in the subgroup of stranger-users. The risk of infection in buddy-users depends upon the stability of the buddy affiliations over time, the HIV transmission efficiency per buddy partnership and the seroprevalence in the subgroup of buddy-users. Stranger-users and buddy-users are not equally represented in the NYC IVDU community, only a small minority of IVDUs are stranger-users (Hartel *et al.* 1988; Hartel *et al.* submitted). Heterogeneity in IVDU behaviour was modelled by including both types of IVDUs. Gender-specific heterogeneity in IVDU behaviour was included by allowing the rate of sharing needles and the rate of change of buddy partners to differ between the sexes.

The model consists of thirty-four ordinary differential equations; the definitions of the parameters are given in table 1. There are ten interacting subgroups of

adults in the model: eight IVDU subgroups and two non-IVDU subgroups in the bridge community male and female non-IVDU sex partners of the IVDUs). The eight IVDU subgroups are defined by a hierarchial stratification of the initial IVDU community at three levels: gender, IVDU behaviour (stranger-user or buddy-user) and sexual behaviour. At the sexual behaviour level, IVDUs are classified into two groups based upon whether they have any new sex partners over the time course of the epidemic. The two groups are 'no new sex partners' or 'X new sex partners', where X is assigned a specific data-based value for each IVDU behavioural group. This sexual behaviour dichotomy was devised because a certain proportion of IVDUs may be sexually inactive, due to a variety of causes including psychological dysfunction and heroin-related depressed libido (Kreek 1983). This hierarchial classification scheme of IVDUs incorporates gender-specific heterogeneity in both IVDU and sexual behaviour, and also ensures that the effects of the different risk factors can be independently assessed. Gender-specific heterogeneity in sexual behaviour is modelled by allowing the rate of change of sex partners to differ in each of the six sexually active subgroups.

(*b*) *IVDU and sexual mixing matrices*

The ten subgroups are linked by either IVDU sharing needles and/or other IVDU equipment) and/or by sexual partner choice; these two mixing patterns are modelled by defining sexual and IVDU mixing matrices. The mixing matrices serve to allocate partnerships; they specify who has sex with whom and who shares needles with whom. Sexual mixing matrices are defined based upon particular assumptions as to how the different subgroups select sex partners. Three subgroups of each sex are sexually active: stranger-users, buddy-users and non-IVDUs. The three-by-three sexual mixing matrices are gender-specific; the coefficients of these matrices ($m_f(i,j;t)$ for females and $m_m(i,j;t)$ for males) are the probabilities that an individual in subgroup i has a sexual partnership with an individual of the opposite sex in subgroup j at time t; subgroups i and j are either sexually active stranger-users, buddy-users or non-IVDUs.

The sexual mixing matrices must meet the following four constraints:

(i) All of the coefficients ($m_f(i,j;t)$, $m_m(i,j;t)$) must be greater than or equal to zero and less than or equal to one.

(ii) The sum of every row in the mixing matrices must equal one or zero.

(iii) The number of male (m) partnerships at any time ($N_{mj}(t)\,c_{mj}(t)\,m_m(j,i;t)$) must equal the number of female (f) partnerships at that time ($N_{fi}(t)\,c_{fi}(t)\,m_f(i,j;t)$) for each subgroup; $c_i(t)$ is the rate of change of sex partners for group i at time t, N_i is the number of sexually active individuals (the sum of the susceptible, infected and AIDS individuals) in subgroup i at time t.

(iv) If the total number of partnerships of any subgroup is zero (either $N_{fi}(t)\,c_{fi}(t)$ or $N_{mj}(t)\,c_{mj}(t)$) then the corresponding mixing matrix coefficients $m_f(i,j;t)$ and $m_m(j,i;t)$) are also zero.

Many different sexual mixing patterns are possible, because individuals can 'mix' with individuals in any of the three subgroups of the opposite sex. These possible sexual mixing patterns lie along a continuum: the extremes of this continuum are perfect positive and perfect negative assortative mixing. Perfect negative assortative mixing is defined as 'like individuals mix only with unalike individuals of the opposite sex', where individuals are one of the three types: stranger-users, buddy-users or non-IVDUs. Perfect positive assortative mixing is defined as 'like individuals mix only with like individuals of the opposite sex'. A perfect positive assortative sexual mixing matrix is equivalent to an identity matrix; the diagonal coefficients are ones and the off-diagonal coefficients are zeroes. Gender-specific perfect positive assortative sexual mixing matrices will only achieved if both the sex ratio and the gender-specific rates of sexual partner change are equal. If these conditions are not satisfied, then positive assortative mixing matrices can be generated, but these matrices are not equivalent to an identity matrix. This type of positive assortative mixing may be defined as 'like individuals mix mainly with like individuals of the opposite sex'. Proportional mixing lies between the extremes of perfect positive and perfect negative assortative mixing. Proportional mixing is defined as 'individuals mix with the opposite sex individuals in proportion to the frequency with which the opposite sex individuals are represented in the sexual community'.

The sex ratio in the NYC IVDU community is highly skewed (3 males: 1 female) (des Jarlais *et al.* 1984; Drucker 1986) and the gender-specific rates of sexual partner change are heterogeneous. These observations and the available data suggest that the sexual mixing pattern in NYC may be characterized as 'like with mainly like' mixing†. Therefore, positive assortative sexual mixing matrices were generated for all of the numerical studies presented in this paper. A computer algorithm was developed to generate these matrices; this algorithm simultaneously maximized the amount of positive assortative mixing in both sexes in all three subgroups at all times throughout the numerical simulations. The epidemiological effects of other sexual mixing patterns (proportional mixing and negative assortative mixing) will be presented in a future paper.

In the model, a single IVDU mixing matrix is defined that specifies the needle-sharing mixing probabilities for both sexes; the coefficients of this matrix specify the probability that the needle-sharing partners practice the same type of IVDU (stranger-use or buddy-use). Therefore, the two-by-two IVDU mixing matrix is equivalent to the identity matrix, and stranger-users and buddy-users form mutually exclusive needle-sharing groups; consequently the only spread of the virus between these two groups is due to heterosexual transmission. This IVDU mixing pattern

† Montefiore Medical Center Group personal communication and unpublished data.

is a simplification of the actual mixing pattern that occurs in the NYC IVDU community; IVDUs generally predominantly practice either stranger-user or buddy-user behaviour, although some individuals will practice both types of behaviour. The epidemiological consequences of more complex needle-sharing patterns that may occur between stranger-users and buddy-users will be presented in a future paper.

3. MODEL EQUATIONS

The following equations specify the model; the parameter definitions are listed in table 1. The rate of change of the population size of susceptible women (X_{1f}) who have the single IVDU risk factor (stranger-user) is:

$$\frac{dX_{1f}}{dt} = -X_{1f} i_f \lambda_i - X_{1f} a_{df}, \tag{1}$$

where i_f is the rate of sharing needles per female, λ_i is the female stranger-users IVDU transmission probability and a_{df} is the non-HIV mortality rate, calculated by assuming an average span for injecting drugs of 35 years. The per capita probability of acquiring HIV from a partner or a needle is the product of the transmission efficiency of the virus (given that the partner or the needle is infected) and the probability that the partner or needle is infected with the virus. The probability of acquiring HIV from sharing needles with strangers per female (λ_i) equals the transmission efficiency of acquiring HIV from injecting with one infected needle (β_{dn}) multiplied by the seroprevalence in the total group of male and female (sexually active and non-sexually active) stranger-users sharing needles at time $t(PS(t))$. It is assumed, throughout the model, that IVDUs with AIDS continue to inject drugs and to be sexually active.

The rate of change of the population size of susceptible women (X_{2f}) who have the single IVDU risk factor (buddy-user) is:

$$\frac{dX_{2f}}{dt} = -X_{2f} j_f \lambda_j - X_{2f} a_{df}, \tag{2}$$

where j_f is the rate of change of drug buddies per female and λ_j is the female buddy-users IVDU transmission probability. The probability of acquiring HIV from sharing needles with buddies per female (λ_j) equals the transmission efficiency of HIV during a buddy partnership (given that the buddy partner is infected) (β_{db}) multiplied by the seroprevalence in the total group of male and female (sexually active and non-sexually active) buddy-users sharing needles at time $t(PB(t))$.

The rate of change of the population size of susceptible women (X_{3f}) who have dual risk factors (sexually active stranger-users) is:

$$\frac{dX_{3f}}{dt} = -X_{3f}(i_f \lambda_i + c_{fs}(t)\, \lambda_{3f}) - X_{3f} a_{df}, \tag{3}$$

where $c_{fs}(t)$ is the rate of change of sex partners per female stranger-user and λ_{3f} is the probability of acquiring HIV from heterosexual transmission per female stranger-user; λ_{3f} equals the male to female heterosexual transmission efficiency per partnership (given that the male is infected) (β_{mf}) multiplied by the weighted seroprevalence ($\sum_i m_f(s, i; t)\, P_m(i, t)$; where $P_m(i, t)$ is the seroprevalence in sexually active males in subgroup i, where i equals stranger-user, buddy-users or non-IVDUs and $m_f(s, i; t)$ is the probability that a female stranger-user has a sexual partnership with a male in subgroup i at time t).

The rate of change of the population size of susceptible women (X_{4f}) who have dual risk factors (sexually active buddy-users) is:

$$\frac{dX_{4f}}{dt} = -X_{4f}(j_f \lambda_j + c_{fb}(t)\, \lambda_{4f}) - X_{4f} a_{df}, \tag{4}$$

where $c_{fb}(t)$ is the rate of change of sex partners per female buddy-user and λ_{4f} is the probability of acquiring HIV from heterosexual transmission per female buddy-user: λ_{4f} equals the male to female heterosexual transmission efficiency per partnership (given that the male is infected) (β_{mf}) multiplied by the weighted seroprevalence ($\sum_i m_f(b, i; t)\, P_m(i, t)$; where $m_f(b, i; t)$ is the probability that a female buddy-user has a sexual partnership with a male in subgroup i at time t).

The rate of change of the population size of susceptible women (X_{5f}) who have the single risk factor (heterosexual transmission) is:

$$\frac{dX_{5f}}{dt} = -X_{5f}\, c_{fn}(t)\, \lambda_{5f} - X_{5f} a_f, \tag{5}$$

where $c_{fn}(t)$ is the rate of change of sex partners per female non-IVDU, a_f is the non-HIV mortality rate (calculated by assuming an average sexually active span of 50 years; therefore non-IVDUs are assumed to live longer than IVDUs: $a_{df} > a_f$) and λ_{5f} is the probability of acquiring HIV from heterosexual transmission per female non-IVDU; λ_{5f} equals the male to female heterosexual transmission efficiency per partnership (given that the male is infected) (β_{mf}) multiplied by the weighted seroprevalence ($\sum_i m_f(n, i; t)\, P_m(i, t)$; where $m_f(n, i; t)$ is the probability that a female non-IVDU has a sexual partnership with a male in subgroup i at time t).

The rate of change of the population sizes of the five subgroups of infected/infectious women are given below (equations 6–10), where v_a is the average duration of stay in the infected/infectious class. A constant rate of progression to disease is assumed, as has been assumed in many other simple deterministic HIV/AIDS models (Anderson 1988; Anderson *et al.* 1986, 1988; May & Anderson 1987; May *et al.* 1989) and v_a is set equal to the average incubation time of the virus.

$$\frac{dY_{1f}}{dt} = X_{1f} i_f \lambda_i - Y_{1f}\left(\frac{1}{v_a}\right) - Y_{1f} a_{df}, \tag{6}$$

$$\frac{dY_{2f}}{dt} = X_{2f} j_f \lambda_j - Y_{2f}\left(\frac{1}{v_a}\right) - Y_{2f} a_{df}, \tag{7}$$

$$\frac{\mathrm{d}Y_{3f}}{\mathrm{d}t} = X_{3f}(i_f \lambda_s + c_{fb}(t)\lambda_{3f}) - Y_{3f}\left(\frac{1}{v_a}\right) - Y_{3f}a_{df}, \quad (8)$$

$$\frac{\mathrm{d}Y_{4f}}{\mathrm{d}t} = X_{4f}(j_f \lambda_j + c_{fb}(t)\lambda_{4f}) - Y_{4f}\left(\frac{1}{v_a}\right) - Y_{4f}a_{df}, \quad (9)$$

$$\frac{\mathrm{d}Y_{5f}}{\mathrm{d}t} = X_{5f}c_{fn}(t)\lambda_{5f} - Y_{5f}\left(\frac{1}{v_a}\right) - Y_{5f}a_f. \quad (10)$$

The rate of change of the population sizes of the five subgroups of AIDS women are given below (equations (11)–(15)), where s_a is the average survival time from diagnosis of AIDS to death.

$$\frac{\mathrm{d}A_{1f}}{\mathrm{d}t} = Y_{1f}\left(\frac{1}{v_a}\right) - A_{1f}\left(\frac{1}{s_a}\right) - A_{1f}a_{df}, \quad (11)$$

$$\frac{\mathrm{d}A_{2f}}{\mathrm{d}t} = Y_{2f}\left(\frac{1}{v_a}\right) - A_{2f}\left(\frac{1}{s_a}\right) - A_{2f}a_{df}, \quad (12)$$

$$\frac{\mathrm{d}A_{3f}}{\mathrm{d}t} = Y_{3f}\left(\frac{1}{v_a}\right) - A_{3f}\left(\frac{1}{s_a}\right) - A_{3f}a_{df}, \quad (13)$$

$$\frac{\mathrm{d}A_{4f}}{\mathrm{d}t} = Y_{4f}\left(\frac{1}{v_a}\right) - A_{4f}\left(\frac{1}{s_a}\right) - A_{4f}a_{df}, \quad (14)$$

$$\frac{\mathrm{d}A_{5f}}{\mathrm{d}t} = Y_{5f}\left(\frac{1}{v_a}\right) - A_{5f}\left(\frac{1}{s_a}\right) - A_{5f}a_f. \quad (15)$$

The model also includes fifteen corresponding equations for males; these equations have the same structure as the equations for females, but contain male-specific values for the IVDU and sexual behaviour parameters (see table 1).

Since the model specifies the rate of change of sexual partnerships and the number of sexually active females ($N_f(t)$) and males ($N_m(t)$), the following heterosexual partnership sum rule has to be satisfied at all times:

$$\sum_i N_{fi}(t)\, c_{fi}(t) = \sum_i N_{mi}(t)\, c_{mi}(t), \quad (16)$$

where

$$N_{fi}(t) = X_{fi}(t) + Y_{fi}(t) + A_{fi}(t)$$

and

$$N_{mi}(t) = X_{mi}(t) + Y_{mi}(t) + A_{mi}(t)$$

and i = sexually active stranger-users, buddy-users and non-IVDUs.

During the course of an epidemic, the number of sexually active individuals will change due to non-AIDS and AIDS mortality; therefore, the rate of change of sex partners must vary with the population size to keep the equation balanced. The heterosexual partnership sum rule may be satisfied by specifying a variety of different mechanisms (Le Pont & Blower, submitted typescript). In the numerical analysis of the discrete version of the model, an algorithm was used that altered the rate of change of sex partners (for each of the three sexually active classes in both sexes) in proportion to the availability of the opposite sex, in the following manner:

$$c_{fi}(t) = c_{fi}(t-1)\,\frac{\sum_j N_{mj}(t)\, c_{mj}(t-1)\, m_m(j,i;t-1)}{\sum_j N_{mj}(t-1)\, c_{mj}(t-1)\, m_m(j,i;t-1)}, \quad (17)$$

where t is the time interval; time steps of one day were used in the simulations.

$$c_{mi}(t) = c_{mi}(t-1)\,\frac{\sum_j N_{fj}(t)\, c_{fj}(t-1)\, m_f(j,i;t-1)}{\sum_j N_{fj}(t-1)\, c_{fj}(t-1)\, m_f(j,i;t-1)}. \quad (18)$$

The rate of change of the population size of the infected babies born to IVDU mothers is:

$$\frac{\mathrm{d}Y_{Bf}}{\mathrm{d}t} = b_d[((Y_{3f}+Y_{4f})\,q_1) + ((A_{3f}+A_{4f})\,q_2)] - Y_{Bf}\left(\frac{1}{v_b}\right), \quad (19)$$

where b_d is the birth rate of IVDU mothers, q_1 is the vertical transmission efficiency in mothers who are seropositive (but without AIDS), q_2 is the vertical transmission efficiency in mothers who have been diagnosed with AIDS and v_b is the average pediatric incubation time. A birth rate for NYC IVDUs of 110

Table 1. *Definitions of biological and behavioural parameters*

(All of the transmission efficiencies are conditional on the fact that the partner or needle is infected with HIV.)

β_{db}	HIV transmission efficiency per buddy partnership	i_f	rate of sharing needles per year (for female stranger-users)
β_{dn}	HIV transmission efficiency per needle injection	i_m	rate of sharing needles per year (for male stranger-users)
β_{fm}	heterosexual transmission efficiency per partnership (female to male)	j_f	rate of change of buddy partners per year (for female buddy-users)
β_{mf}	heterosexual transmission efficiency per partnership (male to female)	j_m	rate of change of buddy partners per year (for male buddy-users)
$c_{fb}(t)$	rate of change of sex partners per year (female buddy-users) at time t	q_1	vertical transmission efficiency (seropositive mother, without AIDS)
$c_{fs}(t)$	rate of change of sex partners per year (female stranger-users) at time t	q_2	vertical transmission efficiency (AIDS mother)
$c_{fn}(t)$	rate of change of sex partners per year (female non-IVDUs) at time t	s_a	mean adult survival time (years)
$c_{mb}(t)$	rate of change of sex partners per year (male buddy-users) at time t	s_b	mean pediatric survival time (years)
$c_{ms}(t)$	rate of change of sex partners per year (male stranger-users) at time t	v_a	mean adult incubation time (years)
$c_{mn}(t)$	rate of change of sex partners per year (male non-IVDUs) at time t	v_b	mean pediatric incubation time (years)

babies per 1000 females per year was used in all the numerical simulations (NYC Department of Health 1985).

The rate of change of the population size of the infected babies born to non-IVDU mothers is:

$$\frac{dY_{BN}}{dt} = b_r[(Y_{5f}q_1) + (A_{5f}q_2)] - Y_{BN}\left(\frac{1}{v_b}\right), \quad (20)$$

where b_r is the birth rate of non-IVDU mothers. A birth rate for NYC non-IVDUs of 147 babies per 1000 females per year was used in all the numerical simulations (NYC Department of Health 1985).

The rate of change of the population size of AIDS babies that are born to IVDU and non-IVDU mothers is:

$$\frac{dA_{BI}}{dt} = Y_{BI}\left(\frac{1}{v_b}\right) - A_{BI}\left(\frac{1}{s_b}\right), \quad (21)$$

$$\frac{dA_{BN}}{dt} = Y_{BN}\left(\frac{1}{v_b}\right) - A_{BN}\left(\frac{1}{s_b}\right), \quad (22)$$

where s_b is the average pediatric survival time from diagnosis to death.

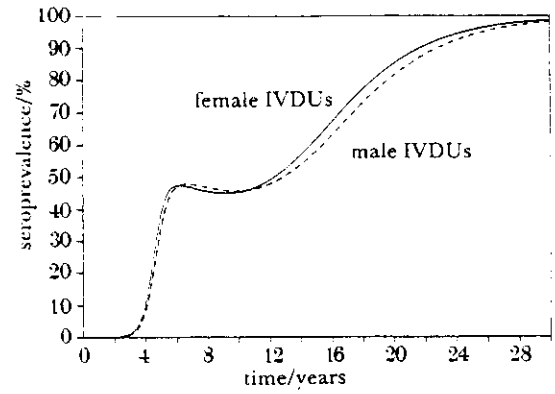

Figure 1. Seroprevalence levels (%) in male and female IVDUs are graphed. The epidemic was begun by introducing one infected male into the sexually active stranger-user category. The text includes a discussion of the estimation of the parameters and the initial subgroup sizes. The initial subgroup sizes, used in the scenario, were: $X_{1f} = 12500$, $X_{2f} = 8250$, $X_{3f} = 12500$, $X_{4f} = 16750$, $X_{5f} = 100000$, $X_{1m} = 63750$, $X_{2m} = 37500$, $X_{3m} = 11250$, $X_4 = 37500$, $X_{5m} = 50000$. The parameter values were estimated from the available data: $\beta_{zb} = 0.5$, $\beta_{zn} = 0.01$, $\beta_{fm} = 0.08$, $\beta_{mf} = 0.24$, $c_{fb}(t) = 1.0$, $c_{fz}(t) = 2.0$, $c_{fn}(t) = 0.57$, $c_{mb}(t) = 1.0$, $c_{mz}(t) = 1.0$, $c_{mn}(t) = 1.0$, $i_f = 300$, $i_m = 230$, $j_f = 0.75$, $j_m = 0.75$, $s_a = 1.0$, $v_a = 8.0$.

4. SCENARIO ANALYSIS

The qualitative behaviour of the model was explored by generating particular scenarios; appropriate values for NYC for the biological-behavioural transmission parameters and the initial sizes of the subgroups were selected from the available data. These computer simulations illustrated that the model could generate a variety of different seroprevalence patterns in the IVDU community. The patterns ranged from a multi-peaked epidemic in the different IVDU subgroups, to a monotonically increasing seroprevalence curve; the particular seroprevalence pattern was dependent upon the values of the biological-behavioural transmission parameters and the (sexual and IVDU) mixing patterns.

A specific scenario is shown in figure 1; the values of the parameters and the initial sizes of the subgroups are given in the figure legend. Seroprevalence levels in the IVDU community rise dramatically, reach a plateau and then stabilize for several years before beginning to rise again (see fig. 1). This temporary stabilization of seroprevalence levels occurred without any change in IVDU or sexual behaviour; it was simply because of the heterogeneity of IVDU behaviour (the eight subgroups of IVDUs had different levels of drug use) and the loose degree of connection between some of the subgroups (i.e. the positive assortative sexual and IVDU mixing patterns). At the beginning of the epidemic, stranger-users were quickly infected by needle-sharing, then HIV slowly seeped into the buddy-user subgroups (due to heterosexual transmission), and finally the virus spread, by heterosexual and IVDU transmission, throughout the buddy subcommunity. In this particular scenario, at the end of 30 years, only 0.03% of non-IVDU women and 0.01% of non-IVDU men were infected. The low amount of heterosexual transmission among the non-IVDUs was the result of the positive assortative sexual mixing pattern. This scenario also generated many more cumulative AIDS cases, at the end of thirty years, in non-IVDU females (3596) than in non-IVDU males (483). This asymmetry in the sex ratio of non-IVDU AIDS cases was due to the asymmetry in the heterosexual transmission efficiencies, the gender-specific differences in sexual behaviour and the asymmetric sex ratio in the IVDU community, (the majority of IVDUs are males, consequently the majority of their sex partners were non-IVDU females).

The history of the HIV epidemic in the NYC IVDU community has been constructed by using a series of seroprevalence surveys (des Jarlais *et al.* 1989). This reconstruction suggests that the epidemic in IVDUs has occurred in three distinct stages: an initial stage when the virus was first introduced and transmission was slow, a secondary stage when the seroprevalence level in IVDUs rose extremely rapidly within a few years, and a tertiary stage when the seroprevalence level stabilized between 50–60% (des Jarlais *et al.* 1989; des Jarlais & Friedman 1988*a*, *b*). Sexual and IVDU behaviour changes have been reported to have occurred in NYC (Chaisson *et al.* 1989; Cox *et al.* 1986; des Jarlais *et al.* 1985; Friedman *et al.* 1987; Selwyn *et al.* 1985) and it has been proposed that IVDU behaviour changes may have effected this stabilization (des Jarlais *et al.* 1989; des Jarlais & Friedman 1988*a*, *b*). However, the epidemiological consequences of behaviour changes cannot be evaluated without a dynamic analysis. Many alternative explanations can explain the stabilization of the seroprevalence level.

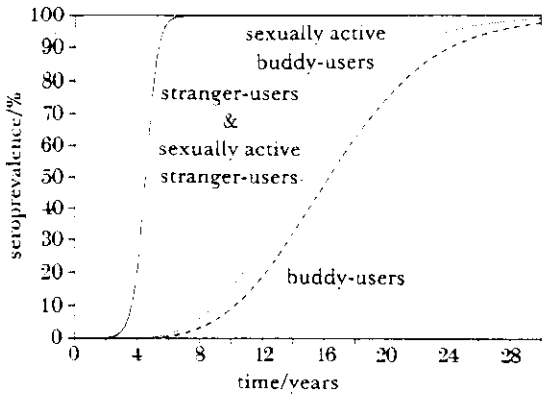

Figure 2. This figure shows the relative effects of heterosexual transmission versus IVDU transmission in female IVDUs. The seroprevalence levels in four groups of IVDUs (stranger-users, buddy-users, sexually active stranger-users and sexually active buddy-users) are graphed. The seroprevalence levels ris at exactly the same rate in both subgroups of stranger-users, but the seroprevalence levels in the two subgroups of buddy-users increase at different rates. The values of the initial subgroup sizes and the biological-behavioural parameter values are given in figure legend 1.

The simulated epidemic in figure 1 closely mirrors the observed seroprevalence pattern in the NYC IVDU community. The simulation results demonstrate that seroprevalence stabilization can occur without any change in IVDU or sexual behaviour; the stabilization of the seroprevalence levels in the simulated epidemic is simply due to the heterogeneity in IVDU behaviour and the (sexual & IVDU) mixing patterns. The simulation results imply that although seroprevalence patterns can be deduced from the transmission dynamics, the causal processes which alter the transmission dynamics should not be inferred from the seroprevalence patterns. If the model provides an adequate explanation of the observed stabilization of the seroprevalence level in the NYC IVDU community, then the simulation results suggest that the current stabilization period may be only temporary and seroprevalence levels may begin to increase.

The computer simulation of the specific scenario shown in figure 1 was also used to examine the gender-specific risks of heterosexual transmission in IVDUs. The results for females are graphed in figure 2 (the results for males were similar, but are not shown); figure 2 was generated by the same set of values for the initial subgroup sizes and the biological-behavioural transmission parameters that were used to generate figure 1. Figure 2 shows that the effect that the heterosexual transmission risk factor has on increasing the risk of HIV infection is dependent upon the level of IVDU. The results for this scenario demonstrate that the addition of the heterosexual transmission risk factor to an individual with a very high risk activity (stranger-IVDU) does not increase the individuals risk of HIV infection. However, the addition of the same risk factor to an individual with a lower risk activity (buddy-IVDU) can significantly increase the individual's risk of HIV infection. These theoretical results are in agreement with the results from a cohort study of IVDUs in NYC, this study has determined that the heterosexual transmission risk is greatest in female IVDUs with the lowest cumulative drug use (Schoenbaum *et al.* 1989).

5. SENSITIVITY ANALYSIS

There is considerable uncertainty in estimating the values of the models' 30 variables: the initial population sizes of the ten subgroups and the twenty biological-behavioural transmission parameters. This degree of estimation uncertainty in the input values ensures that there will be significant variability in the models predictions of the future number of adult and pediatric AIDS cases. Consequently, we performed a sensitivity analysis to assess the variability in these case predictions (i.e. to determine the confidence intervals of the predictions) and to evaluate which were the key variables in contributing to the prediction imprecision. The parameter space of the model is defined by thirty dimensions; each dimension specifies a different variable (initial subgroup size or biological-behavioural transmission parameter), the length of each dimension is determined by the range in the estimates of the value for the particular variable. The Latin Hypercube Sampling/Partial Rank Correlation Coefficient (LHS/PRCC) technique was used, because it is an extremely efficient type of sensitivity analysis that enables the exploration of the entire parameter space of the model, with a minimum number of computer simulations (Blower & Dowlatabadi, submitted typescript). This study is the first application of the LHS/PRCC technique to the analysis of a biological or an epidemiological model; the methodology, advantages and further applications of the technique are described in detail elsewhere (Blower & Dowlatabadi, submitted typescript).

(*a*) *Sensitivity analysis methodology*

The LHS/PRCC sensitivity analysis involved the repeated evaluation of the previously described deterministic model, with all of the variable values varied in each of one hundred runs. The estimation uncertainty for the variables was investigated by specifying a probability density/distribution function (pdf) for each variable; hence, the variability in the pdf was used as a direct measure of the estimation uncertainty for each variable. Each specified pdf described the range of possible values and the probability of occurrence of any specific value for the variable; specific pdfs will be described in detail in a later section of the paper. The model contains 30 variables (10 subgroup sizes and 20 biological-behavioural transmission parameters), however only 24 (5 subgroup sizes and 19 biological-behavioural transmission parameters) were sampled. Only 5 subgroups were sampled, because each of these 5 subgroups was perfectly inversely correlated with one of the remaining 5 subgroups, due to the nature of the subgroup classification scheme. Only 19 parameters were sampled as two parameters were constrained to have the same

value ($\beta_{mf} = \beta_{fm}$), the reason for this constraint will be discussed in a later section of the paper.

A stratified Latin Hypercube sampling scheme was used to select the input values (the values of the variables) for each of the one hundred numerical simulations. To sample the values for each variable, each pdf was divided into one hundred equiprobable intervals; consequently, the sampling distribution of the values for each variable reflected the shape of the particular pdf. Every equiprobable interval of each variable was randomly sampled one hundred times, without replacement. The sampling scheme ensured that the complete range of each variable was sampled (without bias), that every equiprobable interval was used only once, and that the frequency of the selection of the possible values of each variable were determined by their probability of occurrence in the pdf. Furthermore, all of the 24 sampled variables were uncorrelated, because they were sampled by selecting sampling indices along orthogonal vector spaces (see Blower & Dowlatabadi (submitted typescript) for further methodological details). Three biological assumptions were included as constraints at the sampling stage: $q_2 > q_1, \beta_{db} > \beta_{dn}$ and $\beta_{mf} = \beta_{fm}$; these assumptions will be discussed in detail in a later section of the paper, further methodological details of sampling with constraints is given in Blower & Dowlatabadi (submitted typescript). Sampled values were then used as input values for the numerical simulations of the model; the Runga-Kutta 4th order numerical method was used for the simulations. After one hundred simulations had been completed, frequency histograms and descriptive statistics were calculated from two of the model outputs: the cumulative number of adult and pediatric AIDS cases at the end of thirty years.

Non-parametric partial rank correlation coefficients (PRCCs) were then calculated between the input values for each of the 24 sampled variables and the two model outputs. Calculation of these PRCCs enabled the determination of the statistical relationship between each input variable and the specific output variable; these calculations assume that the relationship between each input variable and each output variable is monotonic. The PRCCs allowed the independent effects of each variable to be determined, as they statistically adjusted for the variation produced by all of the other variables; furthermore the PRCCs were not inflated or deflated due to inter-correlations among the variables, because all of the variables had initially been sampled along orthogonal axes.

(*b*) *Estimation of pdfs for the input variables*

Uniform probability density functions were defined for the initial sizes of the ten subgroups; therefore, each interval in the pdf had an equal probability of being sampled. Upper and lower bounds on these pdfs were assigned based upon the available data in the following manner. For each numerical simulation both the initial size and the sex ratio of the IVDU community was kept constant, but the sizes of the IVDU subgroups at the secondary level (type of IVDU behaviour) and the tertiary level (sexual behaviour) were varied. The NYC IVDU community has been estimated to be composed of 50000 women and 150000 men (Frank *et al.* 1978; des Jarlais & Friedman 1988*a*, *b*; des Jarlais *et al.* 1984); hence these values were used to set the initial sex ratio and IVDU community size. Data also suggest that the majority of NYC IVDUs share needles with friends or relatives rather than with strangers in shooting galleries (Hartel *et al.* 1988; Hartel *et al.*, submitted typescript); therefore, the proportion of stranger-users (s) was varied between 0.0 and 0.5 and the proportion of buddy-users (b; $b = 1-s$) was varied between 0.5 and 1.0. The relative proportions of these types of IVDU behaviour were varied independently in men and women. At the tertiary level of sexual behaviour, the proportion of each of the eight IVDU subgroups in the sexually active category was varied between 0.0 and 1.0.

The size of the bridge group has only been crudely estimated; this crude estimate suggests that the size of the bridge group is at least sixty per cent of the size of the IVDU community and may be much greater (des Jarlais *et al.* 1984). In the numerical analysis of the model we assumed that the bridge group was the same size as the IVDU community (200000 individuals). The sex ratio in the bridge community is female-biased (des Jarlais *et al.* 1984), because the sex ratio in the IVDU community is male-biased and hence male IVDUs are more likely than female IVDUs to have non-IVDU sex partners. Therefore, we varied the sex ratio of the bridge community (from 1:1 to 3:1 female-biased) in every run, but we maintained the initial size of the bridge community at 200000 non-IVDUs: therefore, the number of non-IVDU males ranged from 50000 to 100000 and the number of non-IVDU females ranged from 100000 to 150000.

Probability density/distribution functions (pdfs) (with upper and lower bounds) were defined for the biological-behavioural transmission parameters; see table 2 for a full description of these pdfs. It was necessary to construct pdfs for the average values of the adult and pediatric survival times and incubation periods. If a large number of unbiased studies of IVDUs had been conducted, with long-term follow-up periods, then the pdfs could have been constructed simply by plotting out the average values from these studies. However, the few studies that have been conducted have focused on homosexual, haemophiliac-associated or transfusion-associated AIDS cases. Only a few studies have been conducted on the natural history of HIV infection in IVDUs (des Jarlais *et al.* 1987; Fernandez-Cruz *et al.* 1988, 1990; Galli *et al.* 1989; Goedert *et al.* 1986; Rezza *et al.* 1989; Vaccher *et al.* 1989). The results from these natural history studies should be interpreted with caution, due to the small sample sizes and the short follow-up periods. However, the preliminary results from some of these studies suggest that there may be significant differences between IVDUs and other risk groups in the rates of disease progression (Fernandez-Cruz *et al.* 1988, 1990; Galli *et al.* 1989; Schoenbaum *et al.* 1990); other studies have identified an expanded spectrum of HIV-related illness in IVDUs (Schoenbaum *et al.* 1990; Stoneburner *et al.* 1988). These results suggest that there may exist

Table 2. *Parameter density / distribution functions*

Parameter	Min.	Max.	Median	Standard deviation	Function shape
β_{db}	β_{dn}	1	0.56	0.23	triangular (peak at β_{dn})
β_{dn}	0	1	0.28	0.23	triangular (peak at 0.0)
β_{tm}	0	0.5	0.25	0.15	uniform
β_{mf}	0	0.5	0.25	0.15	uniform
$c_{fb}(t)$	1	11	1	1.74	left skewed
$c_{fn}(t)$	1	20	2.19	2.46	left skewed
$c_{fa}(t)$	1	100	2	20.99	left skewed
$c_{mb}(t)$	1	20	1	3.02	left skewed
$c_{mn}(t)$	1	38	2	4.98	left skewed
$c_{ma}(t)$	1	15	1	2.94	left skewed
i_f	13	5265	299	1201	left skewed
i_m	13	3120	228	738	left skewed
j_f	0	4	1.8	0.77	triangular (peak at 1.0)
j_m	0	4	1.8	0.76	triangular (peak at 1.0)
q_1	0	1	0.28	0.23	triangular (peak at 0.0)
q_2	q_1	1	0.56	0.23	triangular (peak at q_1)
s_a	1.0	5.0	1.0	0.85	left skewed
s_b	0.21	4.8	1.04	1.09	left skewed
v_a	1.36	20	8	3.71	Weibull
v_b	0.1	20	0.33 and 5.5	4.99	mixture of two Weibulls

significant differences in the pattern and progression of HIV infection between IVDUs and the previously studied risk groups; these differences may translate into a difference in the average incubation period of HIV in IVDUs. Furthermore, since survival time is related to the clinical manifestation of AIDS, and IVDUs have a different distribution of presenting conditions for AIDS than the distribution that has been found for homosexual men (Schoenbaum *et al.* 1990; Stoneburner *et al.* 1988), then the average survival time in IVDU AIDS cases may differ from the average survival time that has been estimated from homosexual AIDS cases. Therefore, since the appropriate data have not been collected, we used the published data merely as a guide in constructing the necessary pdfs.

The median survival time of adult AIDS cases (estimated from studies of homosexuals and transfusion-associated cases) ranges from 9–13 months (Anderson & Medley 1988; Jason *et al.* 1989; Lemp *et al.* 1990; Harris 1990; Rothenberg *et al.* 1987; Stehr-Green *et al.* 1989; Volberding *et al.* 1990), although some individuals have survived for several years after an AIDS diagnosis. The only published study of survival time of AIDS in IVDUs is based upon 289 spanish IVDUs, the results show that the survival time of IVDU-related AIDS is slightly longer than the estimated survival times calculated for other risk groups (Batalla *et al.* 1989). Consequently, we defined the pdf for the average adult survival time to be left-skewed, with a minimum value of one year and a maximum value of five years; this pdf ensured that there was a much greater probability of shorter than longer survival times, but it also enabled us to investigate the effects of longer survival times. Results of published studies indicate that pediatric survival time may be significantly shorter than adult survival time, although some pediatric cases have survived for several years after an AIDS diagnosis (Anderson & Medley 1988; Rogers *et al.* 1987; Scott *et al.* 1989). Consequently, we defined the pdf for the average pediatric survival time to be left-skewed, with a minimum value of two to three months and a maximum value of approximately five years.

Unfortunately, there are no published studies estimating the average incubation period of HIV in IVDUs. The majority of studies (of transfusion-associated or homosexual AIDS cases) estimate that the average incubation period is in the range of seven to twelve years, but all of these estimates have very wide confidence intervals (Anderson & Medley 1988; Bacchetti & Moss 1989; Hessol *et al.* 1989; Jason *et al.* 1989; Kalbfleisch & Lawless 1988; Lemp *et al.* 1990; Lui *et al.* 1988; Medley *et al.* 1987; Medley *et al.* 1988*a*, *b*). Since the average incubation period in IVDUs may be shorter or longer than in the other risk groups, we used a Weibull distribution for the pdf of the average incubation period. The Weibull that we used ensured that the great majority of selected values were in the seven to twelve year range, but that a few shorter and longer average incubation periods were also investigated. The results of published studies suggest that the incubation period in HIV-infected children is shorter than in HIV-infected adults (Anderson & Medley 1988; Auger *et al.* 1988; Rogers *et al.* 1987; Scott *et al.* 1989). A recent study of the pediatric incubation period suggests that two subgroups of cases may exist: a small subgroup which develops AIDS very quickly and a second much larger subgroup which has an adult-like incubation period (Auger *et al.* 1988). We defined the pdf for the average pediatric incubation period to be bimodal, by adding two Weibull distributions, the two peaks of this function occurred at four months and at five to six years. This pdf enabled us to explore the effects of both short and long average incubation periods; the majority of the probabilities were selected from the

second Weibull. The pdfs for the six remaining biological parameters: IVDU (β_{dn} & β_{db}), heterosexual (β_{mf} & β_{fm}) and vertical transmission efficiencies (q_1 & q_2) are discussed in the biological constraints section.

The calculation of pdfs for the sexual and IVDU behavioural parameters was limited by the availability of the data. Data have not been collected on sexual and IVDU behaviour from large random or representative samples of male and female IVDUs (and their non-IVDU male and female sex partners); such data are necessary to capture adequately all of the gender-specific behavioural heterogeneity. However, the Montefiore Medical Center Group (MMCG) has collected behavioural data from a selected group of IVDUs in NYC, and these data were used to estimate sexual and IVDU behavioural parameters. The MMCG are currently studying a cohort of over 700 IVDUs at a methadone maintenance clinic in a high AIDS incidence area in the Bronx, New York (Hartel *et al.* 1988; Hartel *et al.* submitted; Selwyn *et al.* 1985, 1987, 1988*a*, *b*, 1989*a–d*; Schoenbaum *et al.* 1987*a*, *b*, 1989). Data from the MMCG's study may be fairly representative of a large fraction of the NYC IVDU community, because surveys have shown that the majority of opiate addicts in NYC have had some experience with treatment clinics (Drucker & Vermund 1981). Many of the MMCG's selected IVDUs were in drug treatment at the time of their interview, but their pre-treatment history was obtained. The MMCG data capture a heterogeneous sample of risk behaviours, the MMCG's study participants are current and former opiate addicts; 95% have used heroin intravenously and 70% have also used cocaine. Most patients (89%) have injected drugs for at least two years during the period 1978 to 1987, and approximately 55% of them are still injecting. The median age of the study population is 34 years old (75% are between 30 and 45 years old). There is no evident selection bias between the study participants and other patients as the methadone maintenance clinic; no statistically significant differences were found on the basis of socio-economic class, IVDU behaviour, time in treatment and AIDS incidence (D. Hartel, unpublished data).

The MMCG's study, initiated in 1985, examines subjects at six month intervals to determine the rates of HIV seroconversion, and the development of AIDS and HIV-related disease; data are collected on sexual behaviour and needle-sharing practices since 1978. The needle use data appears reliable (measured by reproducibility in repeat interviews and internal consistency) as well as valid (measured by urine toxicology testing) (D. Hartel, unpublished data). Distribution functions derived directly from the data were used to define the pdfs for the gender-specific rates of needle-sharing and the rates of sexual partner change for the six subgroups of sexually active IVDUs (former IVDUs were used to assess the rates for non-IVDUs). Data had not been collected on the gender-specific rate of change of buddy-users; therefore pdfs were defined for these two variables on the basis of qualitative patterns (MMCG, personal communication). The pdfs for the rate of change of buddy-users were defined to be triangular distribution functions; such functions reflect the expectation that values close to the peak of the triangle are those considered most likely to occur.

(*c*) *Biological constraints*

Three constraints were incorporated at the Latin Hypercube sampling stage of the sensitivity analysis, in order to include the following three biological assumptions: (i) $q_2 > q_1$, (ii) $\beta_{db} > \beta_{dn}$ and (iii) $\beta_{mf} = \beta_{fm}$. These three assumptions are discussed below:

(i) $q_2 > q_1$

Vertical transmission studies are currently being conducted to estimate the probability that the baby of a seropositive woman will be born infected with HIV. Data from these studies suggest that the vertical transmission efficiency in a mother with AIDS (q_2) is greater than in a mother who is seropositive, but without AIDS (q_1) (Anderson & Medley 1988; Goedart *et al.* 1989; Mayers *et al.* 1989; Thomas *et al.* 1989). The vertical transmission studies have produced a wide range of estimates (0.0–0.73) (Anderson & Medley 1988; Blanche *et al.* 1989; Boylan & Stein 1990; Douard *et al.* 1989; European Collaborative Study 1988; Goedart *et al.* 1989; Mayers *et al.* 1989; Ryder & Hassig 1988; Thomas *et al.* 1989). The variability in the results of these studies may be due to the differences in study methodology, the small sample sizes, the heterogeneity in the infectivity of the mother, the biological cofactors, the length of follow-up, the passage of maternal antibodies and the criteria used to define HIV infection. The results from the majority of these studies imply that the vertical transmission efficiency is skewed towards the lower end of the probability scale. Therefore a triangular pdf was used for q_1. The peak of the function was set at zero and the values of q_1 were varied between zero and one; this pdf ensured that the majority of the randomly selected values of q_1 were in the lower end of the probability scale, although some high values were also selected. The pdf for q_2 was conditional on the value for q_1, in order to satisfy the biological constraint $q_2 > q_1$. A triangular pdf was also used for q_2; however, the peak of the function was set at q_1 and the values of q_2 were varied between q_1 and one.

(ii) $\beta_{db} > \beta_{dn}$

By definition, the HIV transmission efficiency through IVDU in a buddy-user partnership (where many needles are shared and given that the buddy partner is infected) (β_{db}) has to be greater than the HIV transmission efficiency for a single injection of drugs with an infected needle (β_{dn}). The values of the transmission efficiencies of HIV through IVDU are hard to determine; β_{dn} has been estimated from the available data on HIV needle-stick studies (Friedland & Klein 1987; Marcus *et al.* 1988), but there are no data from which to estimate β_{db}. The needle-stick studies have assessed the probability of individuals becoming infected with HIV due to accidental needle-

stick injuries; these studies have estimated the transmission efficiency of such needle-stick injuries to be very low (0.0–0.008) (Friedland & Klein 1987; Marcus *et al.* 1988). These needle-stick studies are useful for evaluating the lower bound of β_{dn}, however the actual value of β_{dn} may be significantly greater than the lower bound estimate, due to certain IVDU behaviours that facilitate HIV transmission. IVDUs inject directly into veins and may also deliberately share blood or 'boot' (i.e. draw blood up into a syringe to flush out any of the drug that remains in the syringe from the previous injection, and then re-inject) (des Jarlais *et al.* 1986*a*, *b*). The frequent use of these practices suggest that the transmission efficiency from a single injection of drugs with an infected needle will be significantly greater than the transmission efficiency due to a needle stick injury. Furthermore, the volume of blood that is shared by 'booting' (or 'flushing') can often be a hundred or a thousand times greater than the volume of blood that is transferred due to an accidental needlestick injury (Ho *et al.* 1989; Hoffman *et al.* 1989). Consequently, a triangular pdf was used for β_{dn}; the peak of the function was set at zero and the values of β_{dn} were varied between zero and one. This pdf ensured that high values of β_{dn} were sampled, but that the majority of the sampled values of β_{dn} were at the lower end of the probability scale. The pdf for β_{db} was conditional on the value for β_{dn}, to satisfy the biological constraint $\beta_{db} > \beta_{dn}$. A triangular pdf was also used for β_{db}; the peak of the function was set at β_{dn} and the values of β_{db} were varied between β_{dn} and one.

(iii) $\beta_{mf} = \beta_{fm}$

Sexual partnership studies are being conducted to estimate the values of the heterosexual transmission efficiency per partnership (β_{mf} and β_{fm}) (Anderson & May 1988; Anderson & Medley 1988; Anderson *et al.* 1989; European Study Group 1989; Holmes & Kreiss 1988; Johnson 1988; Johnson & Laga 1988; Padian *et al.* 1987; Peterman *et al.* 1988). These studies generally involve monitoring monogamous couples in which only one partner is infected with the virus and neither partner is exposed to the virus through other risk factors. These sexual partnership studies are the only means to evaluate the heterosexual transmission efficiences; estimates of these efficiencies are extremely heterogeneous (0.03–0.71) (Anderson & May 1988; Anderson & Medley 1988; Anderson *et al.* 1989; European Study Group; Holmes & Kreiss 1988; Johnson 1988; Johnson & Laga 1988; Padian *et al.* 1987; Peterman *et al.* 1988). The variability in the results of these studies may be due to the differences in the study methodology, the small sample sizes, the heterogeneity in sexual practices, the behavioural-biological cofactors, the partnership duration and the specific sexual behaviour changes (e.g. condom use) that occur in the different studies. The results of the studies (that have been conducted in developed countries) imply that the value of the heterosexual transmission efficiency (β) is almost always below 0.5; studies of non-IVDUs suggest that the value of β is skewed towards the low end of the probability scale, but studies of heterosexual transmission in IVDUs suggest that the value of β may be much higher than in non-IVDUs. Furthermore, sexual partnership studies also suffer from a bias in their selection of participants, this bias could result in an under-estimate of the value of β; for example, partnerships in which the index case very quickly infects the partner (i.e. the β is high) will often not be included in partnership studies. Therefore, we used uniform distribution functions for β_{mf} and β_{fm} and we varied the values between zero and 0.5. The results of the sexual partnership studies also conflicts in their conclusion as to whether the efficiency of male to female transmission is greater than or equal to female to male transmission. However, in many of the studies, male to female transmission has been more readily apparent than female to male transmission, because the majority of the index cases have been males. Therefore, both the values of β_{mf} and β_{fm} and the degree of the difference between the two transmission efficiencies remains uncertain. In the sensitivity analysis the two heterosexual transmission efficiencies were set to be equal (future studies will evaluate the epidemiological effects of asymmetric heterosexual transmission).

(*d*) *Results: frequency distributions and descriptive statistics*

The size of the NYC IVDU community has only been assessed once and was very crudely estimated to be 200000 addicts (Frank *et al.* 1978); consequently, we used this estimate in every numerical simulation in the sensitivity analysis. However, because this estimate of the IVDU community was derived by using a flawed methodology and a biased data-base, the estimate of 200000 addicts is probably inaccurate (Blower & Hartel 1989). We also wish to stress that the current model does not contain any IVDU or sexual behaviour changes and that such behaviour changes would probably result in significantly fewer numbers of AIDS cases. Hence, we wish to stress that the qualitative insights that the sensitivity analysis produces are of much greater significance than any of the specific numerical values that are predicted for the future number of AIDS cases.

The frequency distributions of the probable number of cumulative AIDS cases (adult and pediatric) produced by the sensitivity analysis are shown in figure 3. The maximum and minimum of these distributions (see table 3) reflect the likely ranges of possible outcomes, rather than the absolute upper and lower bounds of the system; it is unlikely that any one run in the sensitivity analysis would have the specific combination of parameters to produce the absolute extreme values. The frequency distribution of adult AIDS cases is skewed slightly to the right and the frequency distribution of pediatric AIDS cases is skewed to the left (see figure 3). A scatterplot that relates the cumulative number of adult AIDS cases to the cumulative number of pediatric AIDS cases is shown in figure 4; it may be seen that the variance in the number of pediatric AIDS cases increases as the number of adult cases increases. This pattern is the result of the LHS sampling design: if only a few adults

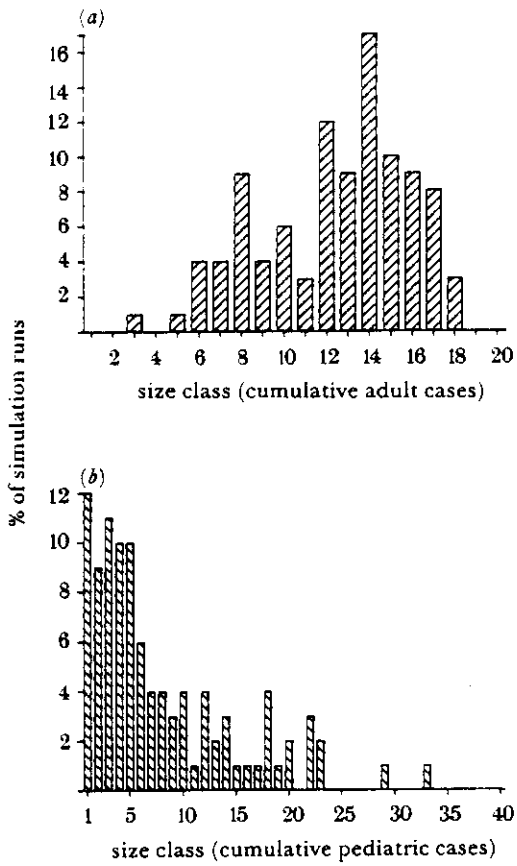

Figure 3. The frequency distributions of the cumulative number of AIDS cases, after 30 years, produced by 100 numerical simulations in the LHS/PRCC sensitivity analysis are graphed for adults (*a*) and pediatrics (*b*). The size class intervals are 20000 AIDS cases in the adult graph; size class 1 contains runs that fall in the range 0–20000. The size class intervals are 5000 AIDS cases in the pediatric graph; size class 1 contains runs that fall in the range 0 to 5000.

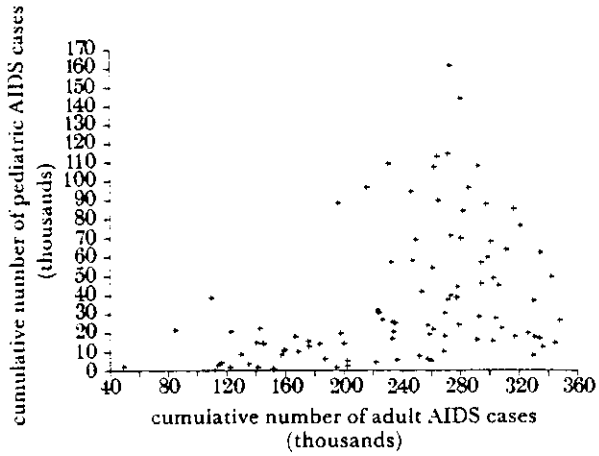

Figure 4. The scatterplot reveals the relationship between the cumulative number of adult and pediatric AIDS cases produced by the 100 numerical simulations for the LHS/PRCC sensitivity analysis.

Table 3. *Descriptive statistics from the sensitivity analysis*

	Cumulative number of aids cases in 30 years	
	Adult cases	Pediatric cases
Minimum	49134	246
Maximum	347420	161615
Mean	238571	37330
Median	257085	22663
Variance	$4.7 * 10^9$	$1.2 * 10^9$
90% confidence intervals	116422–333932	1780–108173

are infected, the number of pediatric AIDS cases are constrained to be low, however, if a large number of adults are infected, the number of pediatric AIDS cases may be either high or low (because the input variables to the model are sampled independently). The frequency distributions of the cumulative number of AIDS cases can be used to assess the probabilities of specific outcomes.

For example, the probability is 0.99 that 30 years after the introduction of the virus, at least 49000 adults with have contracted AIDS, due to either IVDU or heterosexual transmission. The descriptive statistics of the frequency distributions of the cumulative number of adult and pediatric AIDS cases are given in table 3. These statistics and the frequency distributions in figure 3 show that the model can predict a wide range of estimates for the future number of AIDS cases. For example, the 90% confidence interval for cumulative adult AIDS cases is 116422 to 333932. This prediction imprecision is due to the uncertainty in estimating the values of the models' variables. These descriptive statistics and the frequency distributions can not be used to identify which of the input variables are the most important in contributing to the prediction imprecision; consequently, partial rank correlation coefficients (which will be presented in the next section) were calculated in order to identify these key variables.

Approximately 12500 cumulative adult AIDS cases and approximately 550 cumulative pediatric AIDS cases (that are attributed to either IVDU or heterosexual transmission) have been reported to the AIDS surveillance unit in NYC (NYC Health Department 1990). These actual numbers of reported cases can be compared with the number of AIDS cases that are predicted by the model (see table 3)). However, two facts should be considered when the predicted and actual numbers are compared: (*a*) it has been inferred from the reports of the initial AIDS cases that HIV was introduced into the NYC IVDU community in the mid to late seventies (des Jarlais *et al.* 1989; Thomas *et al.* 1988), consequently the actual epidemic is at a considerably earlier stage than the 30 year simulated epidemic. (*b*) The reported AIDS cases may reflect only a fraction of the true HIV morbidity and mortality in NYC IVDUs, due to under-reporting errors and the high non-AIDS mortality rate in IVDUs (Schoenbaum *et al.* 1990; Stoneburner *et al.* 1988). The AIDS case definition was originally devised based upon AIDS cases in homosexual men. It became apparent that IVDUs appear to present with a larger spectrum of HIV-related infections than other risk groups and that therefore the AIDS cases in NYC's

IVDUs were being under-reported (Schoenbaum *et al.* 1990; Stoneburner *et al.* 1988); the AIDS case definition was expanded in 1987. The magnitude of the under-reporting error has recently been assessed by a reevaluation of approximately eight thousand narcotic-related deaths that occurred between 1978 and 1986 (Stoneburner *et al.* 1988). This analysis revealed that narcotic-related mortality due to endocarditis, tuberculosis and pneumonia had significantly increased, concurrently with the HIV epidemic; but that drug-overdose deaths had remained constant. These results were used to suggest a causal association between these diseases and HIV and to propose that the actual HIV-related death rates in IVDUs in NYC may have been twice as high as the reported death rates (Stoneburner *et al.* 1988). Therefore the reported AIDS cases may be expected to be far fewer than the predicted cases due to under-reporting and to the shorter duration of the epidemic; however, it should be noted that the reported number of pediatric AIDS cases (approximately 550) has already exceeded the minimum 30 year predicted value of 246 pediatric cases.

(*e*) *Results: partial rank correlation coefficients (PRCCs)*

The PRCCs were used to identify which were the key variables in contributing to the imprecision in predicting the future number of adult and pediatric AIDS cases; the PRCC results are presented in table 4. The magnitude of the PRCC indicates the importance of the uncertainty in estimating the value of the specific variable in contributing to the prediction imprecision. The sign of the PRCC indicates the qualitative relationship between the input variable and the output variable (cumulative number of adult or pediatric AIDS cases). The order of the ranking of the variables in table 4 indicates the relative importance of the key variables. Different subsets of key variables were identified for the adult and pediatric cases (see table 4).

The PRCCs of eleven of the twenty biological-behavioural transmission parameters and none of the ten initial subgroup sizes are statistically significant ($p < 0.05$) for the adult cases. The values and the rankings of the PRCCs (see table 4) suggest that the uncertainties in estimating the values of three biological-behavioural transmission parameters are the most critical in affecting the prediction imprecision of the future number of adult AIDS cases; these three parameters are the two heterosexual trnsmission efficiencies and the average adult incubation period. The uncertainties in estimating the values of the remaining eight IVDU and sexual behavioural transmission parameters (see table 4) are statistically significant, but are of lesser importance (PRCC $\leqslant 0.35$) in contributing to the prediction imprecision for the adult AIDS cases. These eight parameters are: the IVDU transmission efficiency per buddy partnership, the rates of sex partner change in specific subgroups (female and male non-IVDUs, male buddy-users and male stranger-users, female stranger-users), the rate of sharing needles (for male stranger-users) and the HIV transmission efficiency of a single injection with an infected needle. These results show that sexual and IVDU behavioural parameters, as well as biological parameters are important in prediction imprecision for adult AIDS cases.

The PRCC of eight of the twenty biological-behavioural transmission parameters and two of the initial sizes of the ten subgroups are statistically significant ($p < 0.05$) for the pediatric cases. The values and the rankings of the PRCCs (see table 4) suggest that the uncertainty in estimating the values of four of the biological-behavioural transmission parameters are the most critical in affecting the prediction imprecision of the future number of pediatric AIDS cases; these four parameters are the vertical transmission efficiency, the two heterosexual transmission efficiencies and the average adult incubation period. The uncertainties in the values of six other variables are statistically significant, but are of lesser importance (PRCC $\leqslant 0.36$) in contributing to prediction imprecision for pediatric AIDS cases; these six variables are the average adult survival time, the initial population size of the sexually active female IVDUs (stranger-users and buddy-users), the rate of sex partner change in specific sub-groups (male buddy-users and male stranger-users) and the average pediatric incubation period. These results demonstrate that sexual behavioural and biological parameters, as well as the initial population sizes of the two groups of sexually active female IVDUs are important in prediction imprecision for pediatric AIDS cases.

The sign of the PRCC identifies the specific qualitative relationship between the input and the output variable; the qualitative relationship is the same for all of the key variables, except the average incubation periods. The positive value of the PRCC for the majority of the variable implies that when the value of the input variable increases, the future number of AIDS cases will also increase. The future number of AIDS cases decreases as the average incubation period lengthens, because even though individuals remain infectious for a longer period and consequently can

Table 4. *Partial rank correlation coefficients (PRCCs) calculated from the sensitivity analysis*

(The PRCCs are between the input values of the biological-behavioural transmission parameters and the output values (the cumulative number of adult and pediatric AIDS cases in 30 years). The results are significant at the 0.05 level (*), the 0.01 level (**) or the 0.001 level (***).

Adult cases		Pediatric cases	
Parameter	PRCC	Parameter	PRCC
β_{mf} and β_{fm}	0.84 ***	q_1	0.77 ***
v_a	−0.72 ***	β_{mf} and β_{fm}	0.77 ***
β_{db}	0.35 ***	v_a	0.51 ***
$c_{fn}(0)$	0.29 **	X_{1f}	0.36 ***
$c_{mn}(0)$	0.29 **	$c_{mb}(0)$	0.36 ***
$c_{mb}(0)$	0.25 *	δ_a	0.35 ***
$c_{ms}(0)$	0.23 *	v_b	−0.30 **
i_m	0.22 *	$c_{ms}(0)$	0.28 **
$c_{fs}(0)$	0.21 *	$X_{3f}(0)$	0.20 *
β_{dn}	0.20 *	—	—

infect more individuals, the rate of progression to disease decreases. Epidemiological implications may be inferred from the qualitative PRCC relationships for the key biological parameters, but not for the key behavioural parameters. For example, it may be inferred if average adult survival time is increased, at any time throughout the epidemic, the number of pediatric AIDS cases will increase. This result is of epidemiological relevance, because pregnancy decisions are often independent of HIV sero-status (Selwyn *et al.* 1989*d*), and average adult survival time may now be increasing because of the administration of prophylactic aerosolized pentamidine and other therapeutic drugs, such as AZT and ddI (Cooley *et al.* 1990; Fischl *et al.* 1987; Gail *et al.* 1990; Golden *et al.* 1989; Harris 1990; Lambert *et al.* 1990; Lemp *et al.* 1990; Yarchoan *et al.* 1986). However, decreasing the rate of change of sex partners for male stranger-users, at any time throughout the epidemic, may or may not significantly decrease the future number of adult AIDS cases. The key biological parameters apply to all subgroups, throughout the epidemic; however, the behavioural parameters apply to specific subgroups and may have a time dependent effect by only exerting a significant effect at a specific stage of the epidemic. Consequently, deducing the epidemiological effects of reducing specific behavioural parameters at a midpoint in the epidemic, may lead to erroneous conclusions. The epidemiological effects of behavioural change will be dependent upon both the magnitude, the type and the timing of the behaviour change, and should be investigated through a time-dependent analysis.

6. EPIDEMIOLOGICAL IMPLICATIONS AND CONCLUSIONS

The sensitivity analysis results have significant epidemiological implications. The analysis revealed that the confidence intervals on the prediction estimates of future cumulative numbers of AIDS cases are extremely wide. However, only a few key variables are important in contributing to this prediction imprecision; PRCCs were used to identify and rank the importance of these key variables. Therefore, the results suggest that it is most important to quantify accurately these key variables, and hence the results can be used to suggest a strategic agenda to focus data collection efforts. Reducing the estimation uncertainty in the key biological-behavioural transmission parameters will have a much greater effect on increasing the prediction precision of adult AIDS cases than accurately estimating any of the subgroup sizes. Reducing the estimation uncertainty in the key biological-behavioural transmission parameters will also increase the precision in estimating the future number of pediatric AIDS cases. However, for pediatric AIDS case prediction it is also important to determine the number of sexually active female IVDUs. The PRCC results for pediatric cases highlight the significance of sexually active female IVDUs in the epidemiology of pediatric AIDS in NYC. The magnitude of the effect that reducing the estimation uncertainty of the key variables has on prediction precision will be presented in a subsequent paper.

The model presented in this paper is a simplistic and deterministic model of heterosexual, IVDU and perinatal transmission in NYC. The model was used to provide qualitative insights into HIV epidemiology in NYC and to clarify the relationship between heterosexual and IVDU transmission. Results of the sensitivity and the scenario analysis demonstrated the significance of the dynamic interaction of heterosexual and IVDU transmission. In the early stages of the epidemic, IVDU transmission is often more important than heterosexual transmission; however, the relative importance of heterosexual transmission increases, as the epidemic spreads from the IVDU to the bridge community. The model results suggested a new explanation for the stabilization of the seroprevalence level that has been observed in the NYC IVDU community; the proposed explanation does not rely upon any IVDU or sexual behavioural changes. A computer simulation of a specific scenario was used to examine the gender-specific risks of heterosexual transmission in IVDUs. The results showed that the effect of the heterosexual transmission risk factor on increasing the risk of HIV infection depends upon the level of IVDU. The sensitivity analysis of the model revealed extremely wide confidence intervals in predicting future numbers of adult and pediatric AIDS cases. The analysis revealed that the prediction imprecision was mainly due to the estimation uncertainty of the values of a few key variables; these key variables were identified and ranked by their importance in contributing to prediction imprecision. Long-term precise predictions of AIDS cases will not be possible until these key variables have been determined accurately; however, it is also necessary to develop more realistic mathematical models. Behavioural changes and additional biological complexities, (such as recruitment, more complicated incubation functions, variable transmission efficiencies, age structure and ethnicity) should be included in future models. In the analyses in this paper, we have only investigated the effects of parameter estimation uncertainty for a specified model structure, we assumed positive assortative (sexual and IVDU) mixing patterns. We are currently investigating the sensitivity of our scenario and sensitivity results to the structure of the model (i.e. the specific mixing patterns). In this future analysis, the epidemiological consequences of model structure uncertainty (i.e. the uncertainty in specifying the sexual and IVDU mixing matrices) will be explored and the relative effects of parameter estimation uncertainty and model structure uncertainty will be compared. We hope that this paper has shown the utility of data-based mathematical models in understanding HIV epidemiology and that it may lead to other close collaborations between field epidemiologists and theoreticians. Such collaborations are necessary in order to develop realistic mathematical models that link specific risk behaviours of individuals with the seroprevalence level of a population; the formulation of such models is essential to assess the

epidemiological significance of behavioural intervention strategies.

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The spread of HIV-1 in Africa: sexual contact patterns and the predicted demographic impact of AIDS

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The spread of HIV-1 in Africa is examined here in the light of recent information on the main epidemiological and behavioural determinants of transmission. Mathematical models incorporating demographic, epidemiological and behavioural processes are used to assess the potential demographic impact of the disease AIDS. These analyses highlight the significance of patterns of sexual behaviour, and in particular networks of sexual contact, on the predicted spread of infection. Current data reveal substantial variations in the degree of spread between and in countries, but new analyses support earlier predictions that in the worst-afflicted areas AIDS is likely to change population growth rates from positive to negative values in a few decades.

TEN years after the first description of AIDS[1], the spread of its aetiological agents (the human immunodeficiency viruses HIV-1 and HIV-2[2,3]) continues unabated. In the worst-afflicted regions, such as sub-Saharan Africa, the pattern of spread of these lethal viruses reveals a depressing picture with steadily increasing levels of HIV-1 and HIV-2 infection in the general heterosexual population and very high amounts of infection in the major at-risk groups such as female prostitutes, their male clients and patients attending sexually transmitted disease clinics. In certain urban centres, AIDS is now the leading cause of mortality in adults[4] and one of the main determinants of infant mortality[5]. The extent of spread of HIV-1 in Africa, based on numerous serological surveys over the period 1985–90, is summarized in Fig. 1 and Table 1*a*. In the rest of the world the pattern of spread is very variable between regions, with encouraging evidence of a decreasing rate of growth of the epidemic in male homosexuals in developed countries (after an initial period of rapid spread from 1981 to 1986)[6], continuing rapid spread among intravenous drug users in Europe, North America and parts of South East Asia[7,8], and a slow but steady rise in heterosexual populations in certain developed countries, South America and parts of Asia[9].

Despite much research, there remain many uncertainties in the chief epidemiological and behavioural parameters that influence transmission, due in part to the long and variable incubation period of the disease[10], to the genetic variability of the virus[11] and to the difficulties that surround the study and quantification of human sexual behaviour[12]. Here we examine some of these uncertainties, emphasizing the role of sexual behaviour and contact patterns in determining viral spread, the potential demographic impact of AIDS in Africa, and progress in the development of mathematical models that combine demographic and epidemiological processes in pursuit of better interpretation and prediction.

Epidemiology in Africa

The principal features of HIV-1 spread in Africa are summarized in Fig. 2. Most horizontal transmission events between sexually active adults are through heterosexual contact, with vertical transmission from infected mother to infant being most significant in initiating infection in the youngest age groups. In the general adult population, infection has spread steadily since 1984, reaching 20–30% in the worst-afflicted urban centres as reflected by serological surveys amongst pregnant women and blood donors (Fig. 2*a*). The distribution of infection by age and sex rises steadily as teenagers begin sexual activity, with maximum HIV-1 prevalence in 20–25-year-old women and 25–35-year-old men (Table 1*b*; Fig. 2*b*). This difference is thought to reflect sexual contact of older men with younger women. In the case of HIV-2, peak prevalences are observed in older age classes but the maximum still occurs in women at earlier ages than in men (Fig. 2*b*). The more even spread of HIV-2 infection in older age classes may result from a longer incubation period before disease and subsequent mortality when compared with HIV-1, and/or may reflect a long duration of viral spread in the Guinea-Bissau population referred to in Fig. 2*b*.

The rate of spread in the general urban population differs greatly between regions, being rapid in Malawi, Rwanda, Uganda, Tanzania and Zambia and much slower in Kenya, Mali and Zaire (Table 1*b*). In high-risk groups, such as female prostitutes in Nairobi, transmission has been very rapid (Fig. 2*d*), but not as rapid as in certain intravenous drug-using communities in North America or Thailand (Fig. 2*e*). Patchiness in transmission is reflected by differences in urban and rural areas, such as in Tanzania (Fig. 2*c*), with higher amounts of infection in the former by comparison with the latter. During the past 2 years, however, there has been a steady rise in prevalence in many rural regions (Fig. 1*b*). The differing amounts of infection depend on various factors including the time since the introduction of the infection in a defined area, rates of sexual partner change, patterns of sexual contact between age classes and between individuals in urban and rural populations, and the frequency with which males have sexual contact with female prostitutes. Estimates of the doubling time of the epidemic, as reflected by longitudinal changes in HIV-1 seroprevalence, range from 1 to 3 years in the general populations in the worst afflicted regions, to 5 years or longer in areas where the prevalence is currently low. In female prostitutes in urban centres the doubling time is often 1 year or less (Table 2*a*). But the general pattern in Africa is unclear at present because of poor disease-notification systems (and the fact that at present AIDS cases reflect the rate of viral spread in the highest-risk groups) and the scarcity of reliable longitudinal data (ideally based on cohort studies) on seroprevalence in defined groups (the four most detailed data sets are shown in Fig. 2*a*).

Epidemiological parameters

Information on the main epidemiological parameters determining transmission is slowly accumulating but much uncertainty remains. The major features of infection and disease culled from some of the more extensive studies are summarized in Table 2. In male homosexuals and adult transfusion recipients, roughly

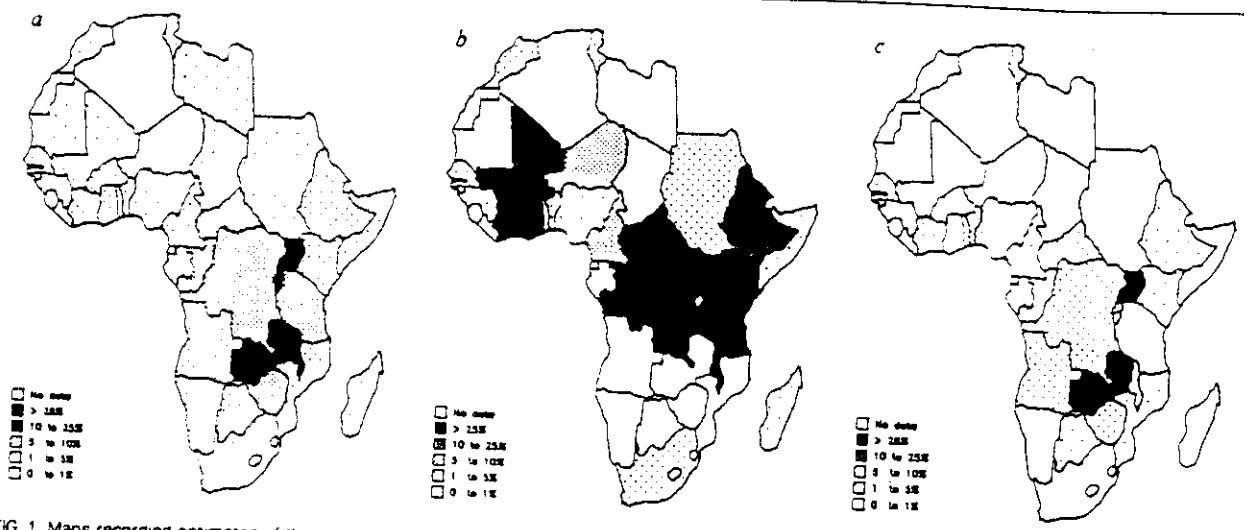

FIG. 1 Maps recording estimates of the prevalence of HIV-1 infection in the heterosexual populations of different African countries. *a*, Sexually active population in urban settings; *b*, female prostitutes (largely in urban settings); *c*, sexually active population in rural settings. The maps are based on numerous published and unpublished surveys of seroprevalence in the general population, pregnant women, blood donors, various occupational groups and female prostitutes recorded in the HIV/AIDS surveillance database[49]. They cover the period 1985–90 and hence probably underestimate the degree of infection in early 1991 as many of the surveys used to compile the maps are 2 or 3 years out of date. The patterns must be viewed with caution given the wide variability in study design and quality between the many surveys used to estimate average prevalence in the defined risk groups. The figures given for a particular country are the weighted (by sample size) average value of all surveys recorded in the database, as detailed in Table 1*a*. The general population refers to seroprevalence in surveys in non-high-risk groups such as pregnant women, blood donors, certain occupational groups and the community in general.

50% have developed AIDS by year 10 of infection, leading to estimates of the mean incubation period (time between first infection to the development of the disease) of between 8–10 years, on the assumption that most of those infected will develop AIDS (which appears likely). This period appears independent of sex or risk-group, but dependent on age[10] and, perhaps, geographical region. There is some evidence from Africa to suggest a much shorter mean period in female prostitutes[13], but other studies do not reveal significant differences from the rates of progression recorded in developed countries[14]. In perinatally infected infants the mean period seems to be between 1 and 2 years[15]. Better treatment and management of asymptomatics in developed countries seems to be increasing the average incubation period[16]. Evidence is emerging that the highly variable incubation period may in part be due to unpredictable (mutation) events determining the emergence of new viral quasispecies with variable cytopathic properties, cell tropisms and replication rates in an infected person[17], and that serious immunodeficiency may be due to viral quasispecies diversity exceeding some threshold beyond which the human immune system is unable to control viral replication[18].

Survival of infants once AIDS (or HIV-related serious disease) is diagnosed is typically less than 1 year, whereas it is between 1 and 2 years on average, and increasing, in adults in developed countries (Table 2*f*). HIV-1-infected mothers in Africa are more likely to have infants that die at or before birth than are uninfected women[19]. Of live births to infected mothers, roughly 40% of infants seem to acquire infection, on the basis of studies in Africa, or roughly 20–30% on the basis of studies in developed countries (Table 2*e*). Much uncertainty surrounds these estimates as some infants remain antibody-positive and antigen-negative, others change from antibody-positive to antibody-negative, whereas others are antibody-negative and antigen-positive[19–23].

Data on the rate of horizontal transmission through sexual contact between heterosexuals is very limited at present because of difficulties in study design and the need to quantify the various facets of sexual behaviour that influence transmission (for example, type and frequency of sexual contact). The transmission probability may be defined per sex act or per partnership, with most studies focusing on the latter with, unfortunately, little information on the likelihood per unit of time, per act or per partner contact. The average pattern recorded in most published studies (see Table 2*d*) suggests transmission probabilities per partnership of 20% from male to female (β_1) and 11% from female to male (β_2). Great variability is apparent in transmission studies and some surveys record equal probabilities[24]. But the apparent average twofold difference between the probabilities of male-to-female and female-to-male transmission may in part explain the observed bias in the sex ratio of HIV-1 infection in Africa where more women seem to be infected than men (1:1.4 male to female ratio)[25,26]. Simple theory suggests that if the effective mean rate of sexual partner change for men is equal to that for women, then the male-to-female ratio of HIV infection is roughly given by $(\beta_2/\beta_1)^{1/2}$ (ref. 27). With values of $\beta_1 = 0.11$, $\beta_1 = 0.2$ (Table 2) this gives a ratio of 1:1.35, which is close to that observed. The likelihood of vertical and horizontal transmission is positively correlated with the severity of disease symptoms in the mother or infected sexual partner (in part reflected by viral or antigen concentration)[28]. It may also be linked with the sporadic emergence of new quasispecies of the virus in the infected person, with the appropriate biological properties that permit transmission.

Sexual behaviour

The higher prevalence of HIV-1 in hetrosexual populations in Africa (by comparison with developed countries) has been linked to its having been spreading for longer there, to much higher prevalences of untreated sexually transmitted diseases (STDs) such as genital ulcers that may promote HIV transmission[29], and to higher rates of sexual partner change in African societies[30,31,90]. Evidence for the first two explanations is growing but that for the third is limited at present (Table 2*g*). The World Health Organization has initiated widescale surveys (KABP questionnaire surveys[32]) on sexual behaviour in Africa and data are beginning to accumulate with surveys in 10 coun-

TABLE 1 Prevalence of HIV in Africa

(a) Weighted mean percentages of the 'general' sexually active urban population with antibodies to HIV-1, based on ELISA tests and other summary statistics

Country	Weighted mean per cent seroprevalence*	Number of surveys	Total number of people tested	Range of seroprevalence estimate	Year of last survey	Estimated urban population size (×100,000)
Algeria	No data					102
Angola	3.6	22	2,366	0.0–16.67	1988	23
Benin	0.12	7	5,046	0.0–0.28	1987	17
Botswana	3.0	3	405	0.0–4.28	1987	2
Burkina Faso	7.3	6	2,222	0.0–10.0	1989	7
Burundi	15.2	2	1,018	4.3–16.3	1986	4
Cameroon	1.0	58	65,523	0.0–10.8	1989	50
Cape Verde	0.04	7	2,496	0.0–0.11	1988	—
C.A.R.	7.5	40	18,177	0.0–17.07	1989	12
Chad	0.0	2	707	—	1986	16
Comoro Islands	0.0	3	995	—	1988	—
Congo	5.7	26	38,864	0.0–24.2	1989	8
Cote d'Ivoire	4.7	68	31,268	0.0–12.99	1989	49
Djibouti	0.2	5	3,336	0.0–2.44	1988	—
Egypt	0.1	16	47,134	0.0–3.7	1989	240
Equatorial Guinea	0.3	2	722	0.26–0.3	1988	—
Ethiopia	2.0	12	14,552	0.0–8.17	1990	54
Gabon	0.5	10	6,559	0.0–1.83	1988	5
Gambia	0.1	3	9,806	0.0–0.12	1989	—
Ghana	3.3	4	1,086	0.0–4.63	1987	44
Guinea	0.3	22	11,049	0.0–1.68	1988–89	16
Guinea-Bissau	0.4	19	11,813	0.0–7.4	1988	—
Kenya	3.4	23	95,335	1.5–25.33	1990	49
Lesotho	0.09	6	10,465	0.0–2.2	1989	3
Liberia	0.3	7	3,929	0.0–0.55	1989	10
Libya	0.0	2	3,064	—	1986–87	27
Madagascar	0.03	10	16,610	0.0–0.04	1989	25
Malawi	17.0	19	7,736	0.0–23.26	1989	10
Mali	0.2	6	1,858	0.0–0.35	1988	15
Mauritania	0.1	13	1,618	0.0–0.41	1987–88	7
Morocco	0.02	5	5,774	0.0–0.03	1984–87	11
Mozambique	3.4	53	44,183	0.0–12.61	1989	34
Namibia	2.1	2	851	0.0–2.54	1988	5
Niger	No data					12
Nigeria	0.3	43	290,302	0.0–1.48	1989	352
Rwanda	21.4	30	11,273	2.98–31.86	1990	4
Sao Tome & Principe	1.0	2	200	0.0–2.0	1988	—
Senegal	0.1	32	27,884	0.0–1.5	1989	26
Sierra Leone	3.5	1	285	—	1987–89	10
Somalia	0.02	9	3,390	0.0–0.07	1988	21
South Africa	0.04	95	5,705,339	0.0–3.76	1990	189
Sudan	0.3	9	31,593	0.0–2.91	1989	49
Tanzania	8.5	47	16,028	0.0–32.81	1989	69
Togo	No data					9
Tunisia	0.08	4	2,667	0.0–0.14	1985–87	41
Uganda	15.2	40	46,208	0.0–33.3	1989	16
Western Sahara	No data					—
Zaire	5.4	83	134,910	0.9–13.42	1989	124
Zambia	13.2	43	19,835	1.96–37.5	1989	38
Zimbabwe	5.6	6	2,110	0.0–36.7	1989	23

(b) Seroprevalence of HIV-1 or HIV-2 in blood donors, pregnant women or the general population in urban areas in Africa, 1987–89

Country	City	Year	Risk group	Sample size	Prevalence (%) (HIV-1 or 2)	Reference
Guinea-Bissau	Bissau	1989	Pregnant women	2,000	(2) 7.0	50
Cote D'Ivoire	Abidjan	1989	Blood donors	2,083	(1) 7.4	51
Kenya	Nairobi	1989–90	Pregnant women	726	(1) 5.4	52
Malawi	Blantyre	1989	Pregnant women	126	(1) 18.3	53
Mali	National survey	1988	Blood donors	1,841	(1) 4.1	54
Mozambique	Maputo city	1989	Blood donors	1,380	(1) 12.6	55
Rwanda	Kigali	1989	Pregnant women	900	(1) 30.3	56
Tanzania	Bukoba	1987	General population	573	(1) 32.8	57
Uganda	Kampala	1989	Pregnant women	650	(1) 31.7	58
Zaire	Kinshasa	1989	Pregnant women	8,108	(1) 6.0	5
Zambia	Lusaka	1989	Blood donors	5,505	(1) 18.8	59

* Weighting based on the sample size of each survey[49].

tries recently completed. The main features of the data are great variability in reported behaviours between and in countries, somewhat higher rates of sexual partner change than those reported in developed countries (perhaps by a factor of 2; see Table 2), higher rates reported by men in comparison with women (perhaps due to exaggeration by men, or to the failure to take account of the sexual contacts made by men with female prostitutes), marked changes in sexual activity with age, and men on average forming sexual partnerships with women younger than themselves[33,34]. The last factor is of particular importance in assessing the potential demographic impact of AIDS, as it acts to intensify transmission in young sexually mature females who potentially contribute most to the net fertility of the population[35]. A recent study in Guinea-Bissau, for

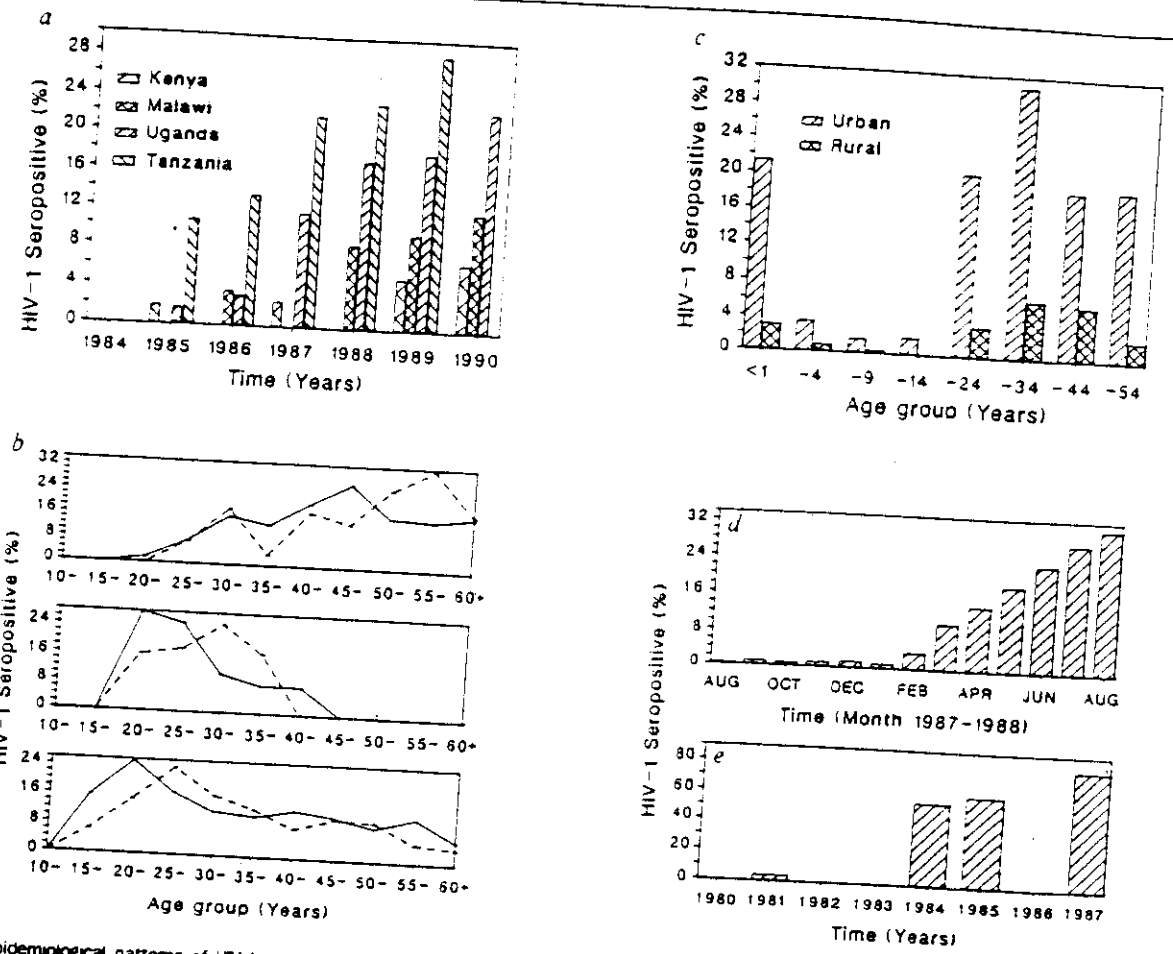

FIG. 2 Epidemiological patterns of HIV-1 and HIV-2 infection in Africa. *a*, Longitudinal (nonconort) trends in HIV-1 seroprevalence over the period 1984–90 in urban pregnant women in Kenya, Malawi, Uganda and Tanzania[49]. *b*, Age and sex stratified seroprevalence surveys of HIV-1 in the general population in Uganda in 1988 (bottom)[66], Zambia in 1985 (middle)[67] and HIV-2 in Guinea-Bissau in 1987 (top)[68]. Male, - - -; female, ——. *c*, Age prevalence of HIV-1 in urban and rural populations in 1987 in the Kagera region of Tanzania[37]. *d*, Spread of HIV-1 in intravenous drug users attending Thanyorak Hospital, Bangkok from August 1987 to August 1988[69]. *e*, Spread of HIV-1 in female prostitutes in Nairobi from 1980 to 1987[60]. Spread is rapid but not as rapid as that for intravenous drug users in Bangkok (*d*).

example, recorded a mean difference of age between man and spouse of 9 years[33]. Heterogeneity in rates of sexual partner change in African societies appears similar in magnitude to that recorded in developed countries where average behaviour (m) is related to variability in behaviour (σ^2) by a power law, $\sigma^2 = am^b$, where a and b are coefficients and the value of b is about 3 (ref. 36). The uniformity in this pattern across widely different societies is difficult to explain. It may be linked to a set of basic rules governing partner formation and dissolution, common to all societies, but the pattern simply states that average behaviour is positively (and supra-linearly) associated with the extremes of behaviour in a given community.

As well as partner change rates and frequency and type of sexual contact in partnerships, the most important processes that determine the pattern of HIV transmission are those governing mixing in or between different strata of the population[37]. These strata include age classes, sexual-activity classes and spatial location (for example urban, rural). There is no information on these processes apart from the general trend for men to form sexual partnerships with younger women. The issue of matching supply and demand for partnerships between women and men is linked to the problem of determining networks of sexual contacts or mixing patterns. For example, if AIDS-induced mortality reduces the number of highly sexually active women (for example, female postitutes), do men reduce their rates of sexual partner contact, do low-activity women increase activity to meet the unfilled demand, or do new female recruits to the prostitute population offset the losses induced by AIDS? In the worst-affected populations, where AIDS is a chief cause of mortality, these issues remain unresolved despite their obvious importance to the future pattern of the epidemic.

Mathematical models

Early work on mathematical models that incorporate epidemiological and demographic processes suggested that AIDS is capable of turning positive population growth rates, of the magnitude of 3% per annum or more, negative over timescales of a few to many decades[27]. The disease selectively acts to increase mortality in young infants (through vertical transmission) and in the sexually active and productive age groups. Models suggest that the overall ratio of productive adults to infants and children (the dependency ratio[27,31,35]) alters little under the impact of AIDS, but at the family level parentless or childless groupings generated by variation in the time sequence of infection and subsequent mortality will create serious social problems. Much controversy surrounded these predictions[34], mainly because many of the early models did not adequately account for heterogeneity in sexual contact between different strata in the population. In the past 2 years, models have been developed that address various aspects of the observed heterogeneity in

TABLE 2 Summary of selected information on the major epidemiological and behavioural parameters that determine the rate of transmission of HIV and the demographic impact of AIDS

(a) Rate of spread of infection as measured by the doubling time (yr) for the prevalence of HIV-1 infection in defined populations in African countries

Country	Risk group	Time period	Doubling time (yr)	Ref.
Kenya	Pregnant women	1985–89	2.8	49
Uganda	Pregnant women	1985–89	2.8	49
Malawi	Pregnant women	1985–89	1.2	49
Kenya, Nairobi	Prostitutes	1981–85	<1.0	60

(b) Sex ratio (male to female) of cases of HIV-1 infection

Uganda	General population	1987	1:1.4	25
Zaire, Kinshasa	Hospital patients	1988	1:1.5	26

(c) Rates of progression from infection to the development of AIDS (a measure of the incubation period of AIDS, and the duration of infectiousness) based on cohort studies

Country	Risk group	Years since infection	Per cent with AIDS	Ref.
ADULTS				
USA	Male homosexuals	11	54	61
USA	Transfusion recipients	8	49	62
USA, Europe, Australia	Male homosexuals	7	39	10
USA, Europe, Australia	Adult haemophiliacs	7	27	10
USA, Europe, Australia	Child haemophiliacs	7	20	10
Sweden	Transfusion recipients	5	22	63
Italy	Intravenous drug users	4	18	64
Kenya, Nairobi	Female prostitutes	3.3	50	13
INFANTS				
USA	Perinatally infected	1.5	59	15
USA	Perinatally infected	1.0	20	65
Europe	Perinatally infected	1.25	42	66

(d) Likelihood of horizontal transmission (percentage who acquire HIV-1 via sexual contact with infected spouse)

MALE TO FEMALE

Country	Sample size	% Spouses HIV-1 positive	Ref.
USA	24	42	67
Europe	155	27	68
Zambia	39	26	19
USA	93	23	69
USA	27	22	70
UK	78	19	71
USA	55	18	72
USA	27	18	73
UK	41	15	74
USA	170	13	75
Sweden	40	10	76
	Weighted average	20%	

FEMALE TO MALE

USA	8	38	67
USA	25	8	72
Zambia	13	8	19
UK	18	6	72

(e) Likelihood of vertical transmission (percentage of babies born to infected mothers with evidence of HIV-1 infection)

Country	Sample size	% with HIV infection or antibodies	Ref.
USA	59	17	77
Europe	272	24	66
USA	55	29	78
Italy	486	33	20
USA	117	35	21
Zaire	92	39	5
Zambia	109	39	19
Europe	372	13–15	22

(f) Survival once AIDS is diagnosed

ADULTS

Country	Sample size	Years	Median survival in months	Ref.
UK*	997	1981–88	10.36	79
USA*	5,833	1981–87	11.4	80

HIV-1 INFECTED INFANTS BORN TO INFECTED MOTHERS

Country	Sample size	Mortality	Ref.
Zambia	42	44% at year 2	19
USA	172	Median survival 3.2 years	23

(g) Sexual behaviour recorded as the claimed number of different sexual partners per defined period of time (heterosexuals, general population surveys)

	Sex	Sample size	Mean (yr^{-1})	Comment	Ref.
UK	Both	523	1.5		81
UK	M	237	1.1		82
UK	F	443	0.89		82
USA	Both	951	2.1		83
Uganda	M	42	2.8	20–34-yr olds	84
Uganda	F	51	1.5	20–34-yr olds	84
Kenya	M	132	11.8		30
Rwanda	M	27	3.0		85
Cote d'Ivoire	Both	—	2.3	Single persons	32
Uganda	M	224	4.0	Rural	86
Uganda	F	506	1.0	Rural	86
Guinea-Bissau	M	152	2.5		33
Kenya	M	134	9.3		30
Kenya	F	152	1.2		30

* Survival times are increasing in developing countries due to the use of AZT and better management of opportunistic infections.

sexual behaviour[31,35]. But theoretical developments have outpaced data availability, given the many practical difficulties associated with the study of sexual behaviour and, in particular, networks of sexual contact. Even so, the theory provides important clues to the interpretation of observed patterns, suggests what data must be acquired, and provides a framework to assess the impact of different control interventions.

Heterogeneity in virus transmission may arise from spatial factors (contacts between villages or urban and rural centres); nonhomogeneous mixing between the age classes of the two sexes or between different social classes, age-dependent changes in sexual activity; and different patterns of mixing between the different sexual activity classes (defined on the basis of rates of sexual partner change). The last factor is of particular importance in determining HIV-1 spread in male homosexual communities in developed countries, where like-with-like (assortative) mixing generates rapid spread, but with infection largely restricted to the small population of highly sexually active individuals, whereas like-with-unlike (disassortative) mixing generates slower spread but a more widely disseminated epidemic[9,40].

In the context of the spatial diffusion of infection, simple

models of sexual contacts in and between villages in rural locations have been used to examine the period over which HIV-1 has been spreading in Africa. Analyses of molecular sequence data from lentiviruses of monkeys (simian immunodeficiency virus, SIV) and humans (HIV-1 and HIV-2) suggest that the human viruses diverged from the monkey strain at least 140–160 years ago[41,42]. Conventional, homogenous mixing epidemiological models find this fact hard to explain (unless R_0 lay infinitesimally above unity for most of this century-long period), but the more complex in-and-between village transmission models suggest that from the initial stuttering chains of transmission events in one village (in which the basic reproductive rate of infection, R_{01}, could be less than unity[27]), the virus can persist through a network of limited sexual contacts between villages, until the combined rate of between- and in-village transmission is sufficient to generate a major epidemic which will only become apparent after a century or more, once infection levels have risen to measurable levels. An illustration of such a calculation is presented in Fig. 3*a*, where for contacts in any one 'seeding' village, $R_{01} < 1$, but overall $R_0 > 1$, due to the summed contributions of contacts between and in villages[43]. In this example, HIV-1 seroprevalence takes 120 years to rise to 20% in the rural villages.

Once the virus has become established, after these initial stuttering chains of transmission events, the doubling time of the epidemic in the general population in the worst-afflicted regions (based on HIV-1 infection, not AIDS cases), appears to lie between 1 and 3 years (see Table 2*a*). Its value will be determined by many factors, but its magnitude will greatly influence the time taken for AIDS-induced mortality to reverse the sign of population growth rates (Fig. 3*b*). Using the model in refs 27, 31, 35, a 1.5-year doubling time reversed the sign of a population growth rate that was 4% before the introduction of HIV-1 around year 30, whereas with a 2.5-year doubling time the period was around 60 years. One of the most important factors determining the magnitude of the net force of infection in the general population is the pattern of sexual contact between the different age classes of the two sexes. Models that take account of the observed bias for men, on average, to form sexual partnerships with women at least 5 years younger than themselves, suggest greatly enhanced demographic impact, when compared with predictions based on restricted in-age-class contact, all other factors being equal[31] (Fig. 3*c*). This results from the concentration of infection in young women of childbearing age and the concomitant impact on infant mortality from AIDS through vertical transmission. This factor, combined with a greater likelihood of transmission from men to women than from women to men (see Table 2) generates predicted age and sex distributions of AIDS cases similar to those observed (Fig. 2*b* and 3*d*). The only major discrepancy lies in a greater number of predicted AIDS cases in young children than that observed. This is probably a consequence of the difficulties surrounding the diagnosis of HIV-1-related infant deaths in regions where other infectious diseases are a major influence on child survival.

The precise patterns of AIDS or HIV-1 infection by age and sex depend critically on the assumptions made concerning the

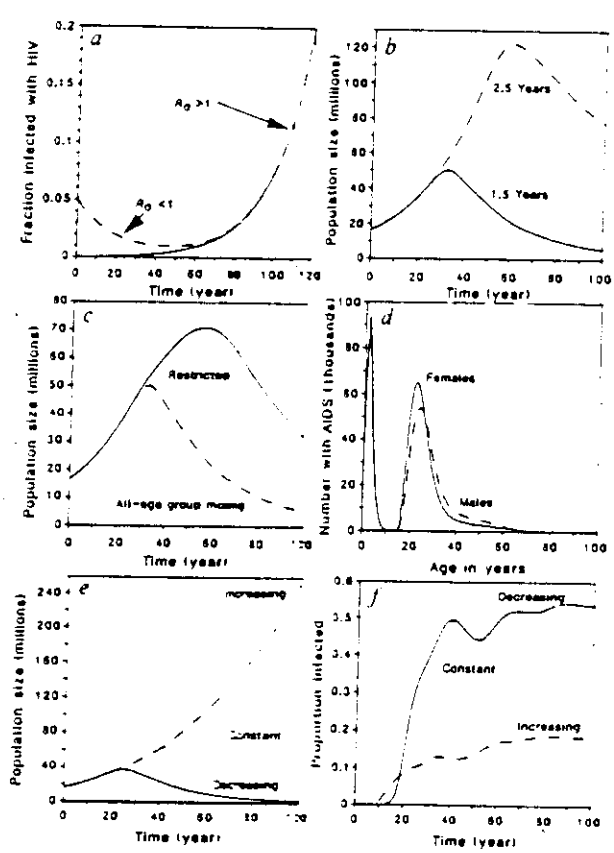

FIG. 3 Mathematical models and predicted patterns of the spread of HIV-1 plus the demographic impact of AIDS. *a*, Predicted temporal changes in the fraction infected with HIV-1 in the village into which the virus was first introduced (the 'seeding' village) and surrounding villages (average village) where sexual contact is predominantly in village but with limited between-village contact[43]. The dashed curve represents the prevalence in the 'seeding' village whereas the solid line denotes the average value in surrounding villages. The basic reproductive rate R_0 was below unity for in-village transmission alone, although above unity for both in and between-village transmission. The initial decline in the levels of infection in any one seeded village, against a rising tide of diffusion of infection among villages is described in ref. 43. *b–f*, Simulations of the demographic impact of AIDS and the spread of HIV-1 infection in a population of 16.6 million (1:1 sex ratio) with a 4% per annum growth rate at time $t = 0$ when HIV-1 was introduced (at a prevalence of 0.1%). The mathematical model, described in refs 27, 35 and 31, is age and sex structured and assumes that the average incubation period of AIDS in adults is 8 years (with variable infectiousness throughout this period) and 2 years in infants infected perinatally, and that the rate of vertical transmission is 50% (a high figure to reflect a high frequency of still births in infected mothers). Male to female transmission was assumed to be a factor of 3 greater than female to male and the probabilities of transmission were adjusted to mirror different doubling times of the epidemic in its early stages in the general population (1.5 years in *c–f*, 1.5 years and 2.5 years in *b*). Rates of sexual partner change per annum were varied in the different simulations as described for each graph as were patterns of sexual contact between the different age classes of the two sexes. Age-specific mortality and fertility rates were set at the start of the simulations to mirror the patterns typically observed in African countries and to give a net population growth rate of 4% in the absence of infection. *b*, Predicted demographic impact on total population size over a period of 100 years for forces of infection on the basis of 1.5-year or 2.5-year doubling time in the early stages of the epidemic. Mixing occurred between all age classes but the pattern was set to mirror men on average, forming sexual partnerships with women 5 years younger than themselves. The rate of sexual partner change was independent of age (3.4 per year at the start of the epidemic). *c*, Influence of the pattern of mixing between the age classes of the two sexes on total population size. In the simulation labelled restricted, males and females only have sexual contact with partners in their own age class. In the simulation labelled all-age group mixing, males on average form partnerships with women 5 years younger than themselves. All other parameters were identical in the two simulations (mean rate of partner change independent of age at 3.4 yr^{-1}). *d*, Age and sex distribution of people with AIDS generated at year 50 in the all-age group mixing simulation in *c*. The pattern generated is very dependent on the assumptions made concerning age-dependency in rates of sexual partner change and the pattern of mixing between the age classes. *e*, Influence of age-dependent changes in the rate of sexual partner change (the same for women and men) on population growth under the assumptions of restricted mixing. Three different assumptions are recorded, the mean increasing with age, the mean constant across age classes and the mean decreasing with age. In all cases the mean over all age classes was held constant at 3.4 yr^{-1} at the start of the three simulations. Aside from age-dependency in sexual activity all other parameters were identical in the three projections. *f*, Predicted temporal trends in the proportion infected with HIV-1 for the three simulations in *e*. The detailed assumptions made in these numerical projections are described in refs 27, 31 and 35.

incubation period of the disease, sexual contact between age classes and age-related changes in sexual activity. Data on the last factor suggest that rates of sexual-partner change are highest in young sexually mature adults and decline in later adult life (perhaps after marriage), with the decline being slower in men than women[33,34]. The precise pattern of age-related change has a large influence on the predicted demographic impact (Fig. 3e). In these predictions (in a population of size 16.6 million and a 4% per annum growth rate, at time $t = 0$ when HIV-1 was introduced) the mean rate of sexual-partner change over all age classes was held constant at 3.4 partners per year, but in the three different simulations the age-specific mean was assumed to be constant, to increase with age, or to decrease with age. The third situation (that observed in survey studies[33,34]) resulted in the greatest demographic impact, as a consequence of focusing infection in young women of childbearing age[31] and in young sexually mature men. The associated temporal changes in the prevalence of infection are recorded in Fig. 3f. Note that in the simulation where the mean is highest in young adults, it is predicted to take 30 years or more before the level of infection approaches 50%, after the establishment of HIV-1 in the population.

A further important source of heterogeneity arises from the pattern of mixing between the different sexual activity classes (based on rates of sexual partner change). The simplest of models, based on the stratification of the population by sex and on two classes of sexual activity (low and high rates of sexual-partner change), illustrates this point[31]. For example, if mixing is set to mimic high-activity men having greatest contact with high-activity women (perhaps female prostitutes), but some contact with low-activity women (who have most contact with low-activity men), then a multiply peaked epidemic may occur, with a rapid epidemic in the small proportion of high-activity men and women and a slower, but larger, longer-term epidemic in the low-activity men and women who constitute the majority of the population (Fig. 4a). The epidemic in the high-activity classes serves to seed the slower growing, longer-term epidemic. Similar patterns may arise with only one activity class of men with moderate levels of sexual activity (but higher than the low-activity class women), where female prostitutes serve to seed the epidemic in most monogamous women through contact with promiscuous husbands. The situations mirrored by these simple models may reflect what is occurring in cities such as Nairobi, where at present levels of infection are high in female prostitutes (60–80%), moderate to high in their male clients (20–40%), and low in pregnant women (5–6%). The low levels in the last group may continue to rise in the next decade, reflecting a second and much larger epidemic in the general population.

The subtle interplay between rates of sexual-partner change, patterns of mixing between sexual activity classes, and the balance between supply and demand of sexual contacts between the sexes could in some circumstances, trigger perverse outcomes if education efforts reduce rates of sexual-partner change in the general population. Consider, for example, the situation where one community has liberal attitudes to the formation of sexual liaisons (such that most people of both sexes have several sexual partners each year and, as a direct result, men have very limited contact with female prostitutes) and a second community in which most women are monogamous but men have many sexual partners per year through frequent contact with prostitutes[31]. If education in the former community reduces partner change rates among women, but, concomitantly, induces men to have more frequent contact with prostitutes, then the result may be an

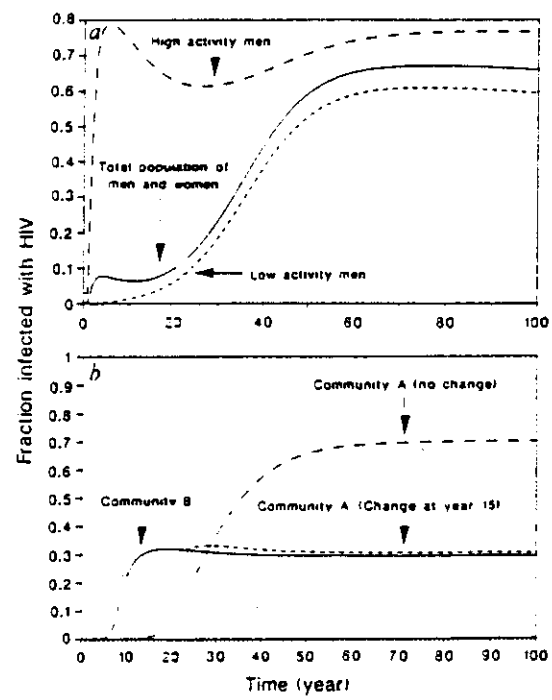

FIG. 4 The influence of sexual contact patterns between different sexual activity classes of men and women (defined on the basis of the rate of sexual partner change per annum) on the pattern of the epidemic. The projections are based on a two sex, two sexual activity class (high and low rates of partner change) model described in ref. 81. *a*, Results of a simulation in which high-activity men (20% of the male population) have frequent sexual contact with high-activity women (prostitutes who form 1% of the female population) and limited contact with low-activity women (99% of the population) (assortative mixing with 99.5% in activity-class contact and 0.5% between activity-class contact). The mean rates of partner change for low- and high-activity men and women were set at 5.0, 20.0 and 4.0, 400.0 per annum, respectively (overall mean for men and women of 8 yr^{-1}). The probabilities of transmission per partner were set at 0.05 for women to men and 0.10 for men to women (yr^{-1}) and the vertical transmission efficiency was set at 40% (incubation period of AIDS of 8 years, with one year survival of AIDS patients, population size of 830,000, a 1:1 sex ratio, and the simulation was started with 4% of high-activity women infected and 3% of high-activity men). The three trajectories record temporal changes in the proportion infected with HIV for the total population (men and women) and high- and low-activity men. *b*, temporal changes in HIV infection in two communities. In community A, the majority of women have several different sexual partners per year such that male contact with very high-activity women (prostitutes, 3.6% of the population) is limited. The mean rates of partner change for low- and high-activity men and women were set at 7.0, 7.0 and 5.0, 60.0 per annum, respectively. (Other parameters are as defined in *a* excepting population size was set at 2×10^6, male to female and female to male transmission probabilites were set equal to 0.05 yr^{-1} and the simulation was started by the introduction of 10 infected high-activity women.) Two simulations are recorded one of no change in behaviour, and one where at year 15, low-activity women reduce their rate of partner change from 5 to 1 yr^{-1}, men keep their rate at 7 yr^{-1}, whereas high-activity women increase their rate to 180 yr^{-1} to meet the increased demand from men created by the change in behaviour in low-activity women. In community B most women (96.4%) have few sexual partners (low activity is 1 partner yr^{-1}) while a few (3.6%) have very many partners (prostitutes with an average of 165.7 partners yr^{-1}). All men have moderate sexual activity (7 partners yr^{-1}) (all other parameters as defined for community A). Note that the spread of infection is limited (rising to a plateau of 30%) and restricted largely to high-activity women and some men.

acceleration in the rate of spread of the virus in the general population in the shorter term. In the longer term, however, the benefits will become apparent by a reduced overall size of the epidemic (Fig. 4*b*). In this example, unless one is aware of the influence of education not only on mean levels of sexual activity but also on patterns of mixing between risk groups, in the shorter term it could be falsely assumed that education was having a detrimental influence on the spread of infection! The uncertain effects of such changes in behaviour on patterns of mixing is somewhat analogous to the problem of understanding how sexual behaviour and mixing are likely to alter as a consequence of AIDS-induced mortality, which is severe in the high-sexual activity classes (that is, matching supply with demand).

Discussion

The current generation of mathematical models of the spread of HIV-1 in Africa reveals a bewildering array of possible outcomes depending on the precise details of sexual behaviour and patterns of sexual contact prevailing in a defined population. The assumed pattern of sexual behaviour dominates the predicted outcome more than small refinements associated with the rates of vertical or horizontal transmission or the duration of the incubation and infectious periods of the disease. Given the lack of quantitative behavioural data, particularly data concerning patterns of sexual contact between age classes, sexual-activity classes (risk groups) and between urban and rural population centres, it is not possible to make precise predictions about the likely demographic impact of AIDS over the coming decade in any one country.

Although model development has outstripped data availability, we believe a few general pointers emerge from recent theoretical work. Simple models based on random mixing between sexual activity classes and restricted mixing in age classes suggest that, with realistic assumptions concerning the major epidemiological and demographic parameters (such as doubling times in the general population between 1 and 3 years), AIDS is able to reverse the sign of population growth rates over timescales of a few to many decades[27,44,45]. The added refinements of age-dependent changes in sexual behaviour, men having sexual contact with women younger than themselves and not infrequent male contact with a small proportion of women with high rates of sexual-partner change, all serve to accentuate the predicted demographic impact, with the only significant uncertainty being whether AIDS induced mortality will decrease population size over a few or many decades. We therefore continue to interpret the available facts as telling us that, in the absence of major changes in behaviour or the development and effective distribution of better drugs or a vaccine, AIDS is likely to induce significant demographic changes in some African countries. The fact that the disease already appears to be the leading cause of adult mortality in certain urban centres in Africa lends support to this conclusion.[4]

What can be done to reduce the spread of infection? A priority at present must be to acquire better data on patterns of sexual behaviour (both rates of partner change and mixing patterns), not only to improve interpretation and prediction, but, more important, to help target education and the distribution of condoms to the groups where they will have the most beneficial impact. For example, frequent use of condoms by female prostitutes and their male clients could delay or even prevent a more widely disseminated epidemic among the general population in countries where infection in high-risk groups is low to moderate at present (for example, Nigeria). In addition, the growing body of evidence that points to the importance of other sexually transmitted diseases (STDs) in enhancing the likelihood of transmission of HIV[29,46], argues for greatly increased efforts to treat and control STD spread in general. Simple models of concomitant STD and HIV transmission lend support to this approach, provided the degree to which the other disease enhances HIV transmission is sufficiently large[47]. A further advantage of greater effort in general STD control is that su programmes facilitate counselling and condom distribution a high-risk segment of the population. Models can also be us to assess the likely influence on the rate of spread of infecti of different degrees of behaviour change or frequency of condc use, in relation to the timing of the introduction of su behaviour changes in the course of the epidemic. The effects timing are important, and not intuitively obvious, given t nonlinear character of the epidemic. But the general conclusi is that changes introduced earlier on in the course of the ep demic have a disproportionately greater effect than simil changes introduced later[48]. Therefore, even when levels of HI infection are low in the general population and AIDS is not th leading cause of mortality in countries afflicted by many othe serious diseases, significant resources should be directed toward inducing behavioural change to try to prevent a widely dissem nated lethal epidemic in 10–20 years time. Models that cha the slow but continuous development of the epidemic over man decades are important in convincing governments and inter national agencies to take this course, despite many more obviou and immediate public-health priorities.

Future epidemiological research needs are many but th immediate concerns must lie with the scientific assessment o different strategies of intervention, concomitant with quantita tive studies of behaviour to assess sexual activity and mixing both before and after a given intervention. It is vitally importan that, in addition to measuring success through changes in rate of infection (which are difficult to interpret, given the nonlinear nature of epidemics), emphasis is placed on assessing precisely who changes behaviour. More generally, Tables 1 and 2 highlight the need for better longitudinal data on seroprevalence (ideally from cohorts), estimates of incubation and infectious periods, and studies of the probabilities of vertical and horizontal transmission, all in African settings.

Epidemiological research in Africa and elsewhere has tended to be on a small scale, with little emphasis on the standardization of study design and methods. The successes of multicentre cohort studies in the United States and Europe involving many patients suggest much could be gained in Africa by encouraging carefully designed multicountry studies using standard methods. Some progress has been made in this direction by the WHO in sexual-behaviour research, but more emphasis is likely to be of great benefit in other areas of the epidemiological study of AIDS. But the growing suspicion that genetic variability in viral populations, both in and between infected individuals, is a major influence on the likelihood of transmission and the development of disease will necessitate the addition of molecular virological techniques to the already difficult problems of studying transmission events that involve highly variable patterns of human sexual behaviour. □

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Ancient oceans, ice sheets and the hydrological cycle on Mars

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A variety of anomalous geomorphological features on Mars can be explained by a conceptual scheme involving episodic ocean and ice-sheet formation. The formation of valley networks early in Mars' history is evidence for a long-term hydrological cycle, which may have been associated with the existence of a persistent ocean. Cataclysmic flooding, triggered by extensive Tharsis volcanism, subsequently led to repeated ocean formation and then dissipation on the northern plains, and associated glaciation in the southern highlands until relatively late in martian history.

MARS is the only planet besides Earth known to have had a long-term dynamic hydrological cycle. Despite its modern cold, dry climate and extensive areas of heavily cratered terrain left over from ancient times, Mars shows abundant evidence for the action of water and ice earlier in geological history. This includes fluvial dissection[1,2], periglacial landforms[3,4], ice-related permafrost[5,6], lacustrine features[7,8], possible phased degradation of impact craters[9] and possible glacial landforms[10]. The most spectacular fluvial features on the planet are the immense outflow channels, which originated by cataclysmic outbursts of water from subsurface sources[11,12]. The largest outflow channels are concentrated in the Chryse trough on the eastern margin of the Tharsis bulge. The channels nearly all debouched their flood water to the northern plains of Mars, where ponded sediments[13,14], shoreline indicators, infilled craters and basins, spillover channels[15], pitted basin floors, whorled patterns of multiple ridges and other evidence indicate the past existence of extensive lakes[15] or temporary regional flooding[16].

Parker *et al.*[17] presented evidence for the sporadic formation of a great ocean covering the northern plains of Mars, which we name Oceanus Borealis. Features related to the inundation of the northern plains and the outflow channels all belong to the Hesperian and Amazonian geological systems[18]. These time-stratigraphic designations (the Hesperian is the older, the Amazonian the younger system) both occur after the period of heavy bombardment, corresponding to the Noachian geological system[18], which ended $\sim 2.8–3.8 \times 10^9$ years ago[19]. Here we propose a conceptual scheme in which Oceanus Borealis repeatedly forms and dissipates, temporarily producing a relatively warm,