

Risk behavior-based model of the cubic growth of acquired immunodeficiency syndrome in the United States

(human immunodeficiency virus/epidemiologic model/polynomial growth)

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ABSTRACT The cumulative number of cases of acquired immunodeficiency syndrome (AIDS) in the United States has grown as the cube of time rather than exponentially. We explain this by interactions involving partner choice and sexual frequency in a risk-behavior model with biased mixing. This leads to a saturation wave of infection moving from high- to low-risk groups. If this description is correct, then the decreasing growth rate of AIDS cases is not due to behavior changes; rather it is due to the intrinsic epidemiology of the disease.

Understanding the growth of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) is complex because infection depends on behaviors that are considered private and because individuals with HIV vary in their infectivity and progression to AIDS. Previous mathematical models predict an initial exponential growth of infection ultimately progressing to saturation of the population. In this article, we develop a model explaining the observed cubic growth of AIDS and apply it to the homosexual population.

The risk-based model builds on the fact that the amount of "risky" behavior (sexual behavior that puts one at risk for contracting HIV) is not distributed equally among the population. It also assumes that people with similar risk behavior tend to interact primarily among themselves (biased mixing) rather than equally with others (homogeneous mixing). Finally, the model incorporates epidemiologic data on the progression from initial HIV infection to AIDS.

The total number of AIDS cases reported to the Centers for Disease Control (CDC) in the United States has grown as the cube of time (1-3). A reasonable best fit function for the cumulative AIDS cases (pre-1987.5 definition) is

$$A = 174.6(t_y - 1981.2)^3 + 340 \pm 2\%, \quad [1]$$

where the error is relative to total cases and t_y is the date in years (see Fig. 1). This fit is accurate between $t_y = 1982.5$ and the change in AIDS case definition in 1987. Nearly cubic growth is evident in different geographic regions, sexual preference groups, intravenous drug users, age groups (except children and elderly), and racial groups. Eq. 1 is surprising, since a cubic sum for all AIDS cases of the form in Eq. 1 requires that the cubics for each major infected group be synchronized in time to less than 6 months. Because there are no large populations in the United States without infected persons (1, 4, 5), this synchronization applies to standard metropolitan statistical areas as well.

To demonstrate why this cubic growth is unexpected, we note that the initial growth rate of any infection in a homogeneous population (where behavior remains constant in time) will be constant with time. In contrast, cubic growth of

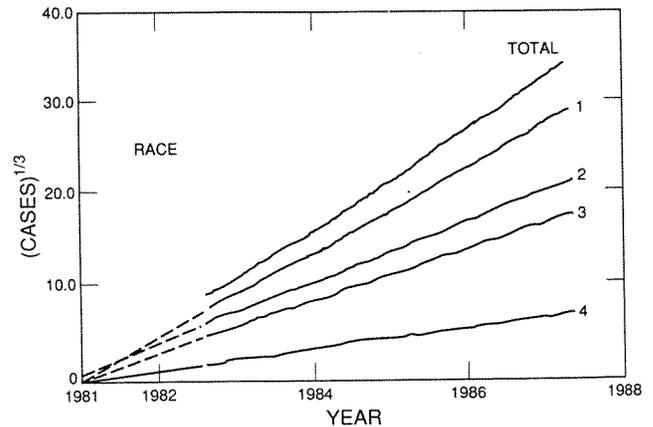


FIG. 1. Cumulative AIDS cases plotted as the cube root versus time as reported by the CDC (date in years). Data for years prior to 1982.5 are statistically unreliable and, therefore, not shown. The data are adjusted to account for increased reporting delays in 1987. The best fit, $A = 174.6(t - 1981.2)^3 + 340$, shows that AIDS cases grew as a cubic polynomial between 1982.5 and 1987.5. Also shown are the cumulative data broken down into subgroups according to race and plotted as the cube root versus time: 1, White; 2, Black; 3, Hispanic; and 4, unknown. The dotted lines are an extrapolation of the cubic slope, indicating that the various sexual preference groups were seeded within a 6-month window. This implies that at least one individual in each of the four sexual preference groups was a member of the original high-risk group ($t_d = 6$ months). Four racial categories as well as the standard metropolitan statistical areas also reveal the same cubic behavior.

AIDS implies that the growth rate is decreasing inversely with time. In Eq. 1, if $t = t_y - 1981.2$, then $A = A_0 + A_1 t^m$ and the relative growth rate $= (dA/dt)/A \cong m/t$, where m is a constant for polynomial growth. With polynomial growth, not only does the relative growth rate decrease inversely with time but also the doubling time (the time for the number of people diagnosed with AIDS to double) increases proportionally with t . The doubling time, t_d , associated with a generalized growth rate, $(dA/dt)/A$, is $t_d = (\ln 2)A/(dA/dt)$; hence, using the above approximation gives $t_d = t(\ln 2)/m$ years. For AIDS cases observed so far, $m = 3$ and the next doubling time is given by $t_d \cong t/4$ years. The epidemic started with $t_d < 0.5$ year (6) and progressed to the value of $t_d \cong 1.8$ years in 1988. This increase in doubling time by more than 4-fold is significantly different from epidemics with exponential growth.

The perception that an increasing doubling time of AIDS cases reflects effective education and decreasing participation in risk behavior must be carefully examined. If learning had modified risk behavior inversely as a function of time, the resulting growth would be polynomial. However, AIDS cases

in the early-to-mid 1980s reflect initial HIV infections in the late 1970s and early 1980s (5), which is long before learning affected a major fraction of the homosexual population. Behavior changes would not be large enough to result in t^3 growth.

Another possibility is that the growth of HIV infections is exponential and the transition times from infection to AIDS are highly variable. However, this does not result in t^3 growth, since a sustained exponential growth of infection converting to AIDS in a finite time ultimately results in exponential growth of AIDS cases. (An initial t^3 growth could occur but would require an unrealistic conversion time from infection to AIDS.)

After considering a number of ways to produce a constant polynomial growth, we conclude that a biased mixing model best fits the CDC AIDS case data. The model we develop extends an earlier risk-based model by May and Anderson (6-9), where homogeneous mixing of the susceptible population resulted in an early exponential growth. The discrepancy between early exponential and polynomial growth led us to develop this biased-mixing model (2, 3).

THE MODEL

For our model to agree with the growth of AIDS cases, assume that groups of similar risk behavior, r , interact primarily but not exclusively within themselves. Also assume that risk behavior is distributed so that the number of individuals decreases as a function of risk. Finally, assume that the initial infection rate within a group of risk behavior r is proportional to r . Because the most extensive epidemiologic data pertain to homosexual men, we restrict our analysis to two related risk behaviors—new partner rate and frequency of sexual contact (10-12). This limits our analysis to the homosexual epidemic or roughly 65% of the AIDS cases (1).

Several studies of homosexual men provide data on the number of new sexual partners with time (6, 13-15). For men with more than a few partners per year, the distribution $p^{-\beta}$, where p is the number of new partners per year and $3 \leq \beta \leq$

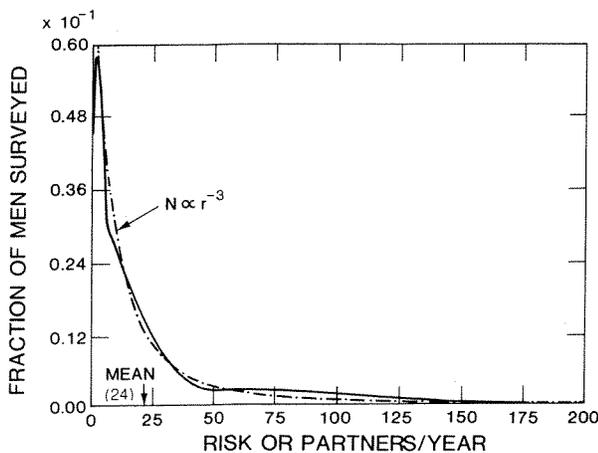


FIG. 2. Distribution of new-partner rate for homosexual men attending sexually transmitted disease clinics in London. The graph is generated by combining the data of T. McManus (partners per year) and C. A. Carne and I. V. Waller (partners per month) (6). The broken line shows the inverse cubic slope with the same mean as the data, $2 \langle p \rangle^3 / [\langle (p) \rangle + p]^3$. These two studies are biased toward high-activity men. Other randomly chosen samples (14, 15) have the same $p^{-\beta}$ behavior for large p , but with a larger fraction of the sample at low p . The variance of the distribution, $\sigma / \langle p \rangle = 12$ for the raw data, is well approximated when $\beta = 3$. If $\beta = 4$, $\sigma / \langle p \rangle = 4$, which is a poorer fit.

4 gives a good fit to the data. Fig. 2 shows combined data from two studies of homosexual men attending sexually transmitted disease clinics in London by T. McManus and by C. A. Carne and I. V. Waller as reported in ref. 6, as well as the fit $2 \langle p \rangle^3 / [\langle (p) \rangle + p]^3$, where $\langle p \rangle$ is the mean number of partners. Although these two studies are biased toward high-activity men, other randomly chosen samples have the same $p^{-\beta}$ behavior for large p but have a larger fraction of the sample at low p (14-16). To be consistent with the sexual frequency data of Kinsey *et al.* (ref. 17; see below), we choose $\beta = 3$ for all of our calculations.

Fig. 3 shows the frequency of sexual outlet data from Kinsey *et al.* (17) for a sample of 11,467 males from adolescence to 30 years old. The data are plotted as the number of people versus frequency per week on a log-log scale. The distribution superimposed on the data in the figure is

$$N/N_0 = (f/\langle f \rangle)^{-3} \quad \text{when } f \geq \langle f \rangle \quad [2a]$$

$$N/N_0 = 1 \quad \text{when } f < \langle f \rangle, \quad [2b]$$

where $(3/2)N_0$ is the total sample size and $\langle f \rangle$ is the population mean. The distribution for sexual outlet frequency among the U.S. male population clearly resembles the distribution for new partners among homosexuals. A positive correlation between outlet frequency, contact frequency, new partner rate, and hence, risk of infection is assumed.

Divide the population into groups with similar risk behavior and let r denote the rate of this risk behavior divided by the mean. The procedure normalizes the risk for the average group to be $r = 1$. Assume that members of a particular risk group interact primarily among themselves (intragroup preference) and that within each group the mixing is homogeneous. After a group is seeded by one HIV infection, the number of new infections grows exponentially, and the growth rate within the group is proportional to the group's normalized risk behavior, r .

The assumption that the growth of new infections is proportional to risk implies that the time for each group to

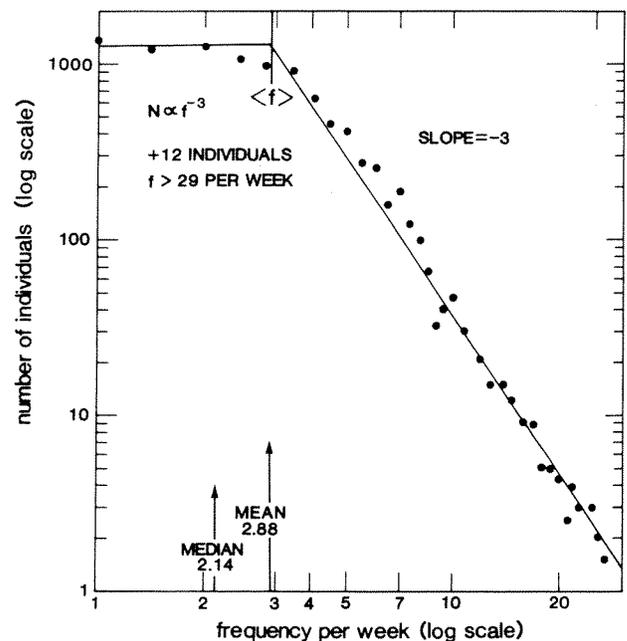


FIG. 3. The distribution of males (adolescent to 30) versus sexual outlet frequency. Data are plotted as the number of individuals versus frequency per week, f , on a log scale. A line with a negative slope = -3 is a reasonably good fit to the data above the mean, $\langle f \rangle$, demonstrating that the distribution above the mean is inverse cubic. The data are from Kinsey *et al.* (17).

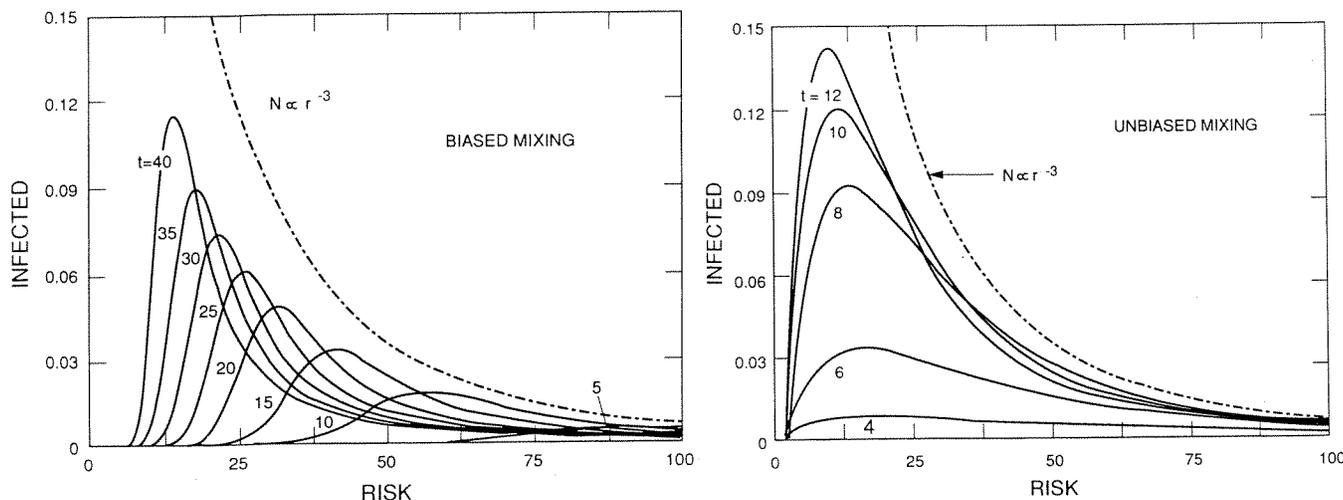


FIG. 4. (Left) Calculation of the fraction infected versus risk behavior at various times ($t = 10, 15, 20, \dots, 40$ in arbitrary units) when mixing is biased. After the individual with the highest risk behavior ($r = 174$) is infected at $t = 0$, the infection grows to saturation in the highest risk groups and moves progressively to lower risk groups. The distribution in risk behavior among the population, $N(r)$, decreases as r^{-3} (broken line). The sum of all those infected grows as t^2 . These numerical results were generated by using our general model. The out-of-group mixing fraction, F , was modeled by a Gaussian curve, whose full width at half maximum was 40% of the risk behavior r . The fraction infected is always below the broken line because individuals with AIDS are removed from the fraction infected. (Right) Numerical results of the model with homogeneous mixing ($F = 1$). Again, the earliest infected individuals are in the highest risk group. In contrast to biased mixing, however, the fastest growth of infection occurs in the average risk behavior group, contrary to CDC observations. Early growth is nearly exponential and the number infected at any time is larger than the biased-mixing case, because a smaller fraction is saturated.

reach saturation is inversely proportional to r . Thus, high-risk groups saturate much more quickly than low-risk groups. The fact that groups with large r have fewer members decreases the saturation time still further; that is, the saturation time is proportional to $r^{-1} \log[N(r)/N_s(r)]$, where N_s is the number of individuals infected (seeded) before the start of the saturation wave. Because the logarithm function varies slowly, the r^{-1} dependence dominates the time to saturation. After a member of the highest risk group becomes infected, that group quickly saturates; then the next lower group saturates, and so on. Out-of-group mixing causes progression of the infection to be more diffuse. Infection occurs as a saturation wave in risk behavior.

Fig. 4 Left shows a saturation wave of infection progressing from high-risk to low-risk groups, calculated numerically from the general formulas for the risk-based model (3). To the right of the wave front, individuals are infected with HIV. They are removed from the calculation as they develop AIDS or die. To the left of the front, few low-risk individuals are infected. New infections occur primarily in the group at the wave front and the doubling time of the epidemic is essentially the doubling time of this leading group. In this calculation, most of the contacts are between individuals within the same group. There is a small fraction of out-of-group contacts, F . This both reduces the growth rate within a group by $1 - F$ and increases the growth rate in neighboring risk groups. Fig. 4 Right shows what happens if homogeneous mixing is assumed—i.e., $F \rightarrow 1$. Because there are far more people at low risk than high risk, new infections occur primarily in the low-risk population, and the cumulative growth is exponential.

Once the saturation wave begins in Fig. 4 Left, the total number infected, I , is approximated by summing over all individuals from the highest risk down to those with risk behavior r_* at the wave front. Neglecting the few infected individuals that were “seeded” throughout the population before the wave began, the sum of the saturated groups is the integral of all individuals with risk behavior $r \geq r_*$:

$$I(r_*) \cong \int_{r_*}^{\infty} N(r) dr = (N_0/2)r_*^{-2}, \quad [3]$$

where r_* is the behavior of the lowest risk group that has most of its members infected, and $N(r)$ is the number of individuals with risk behavior r given by Eq. 2a. In risk group r_* , the growth rate of infection is αr_* , where α is proportional to the transmissibility of HIV per contact and is assumed to be constant.

Thus, the infection initially grows as $I_s e^{\alpha r_* t}$, where I_s is the number of individuals “seeded” by $t = 0$, the start of the saturation wave. The time, t , of the infection process is relative to the AIDS process, where we already defined $t = 0$ at 1981.2 in Eq. 1. At saturation, the total number infected in the group r_* approaches the total number in the group, $N(r_*)$, so that for exponential growth $N(r_*) \cong I_s e^{\alpha r_* t_*}$, where t_* is the time to saturate the r_* group. Thus, solving for t_* gives $t_* \cong (1/\alpha r_*) \ln(N_*/I_s)$. If we assume the logarithm of group size to seed ratio, $\ln(N_*/I_s)$, to be approximately constant—i.e., all risk groups were seeded before individuals in the highest risk group started the saturation wave, then the time t_* to saturate a group with risk r_* is proportional to $1/r_*$. Hence, the time to saturate a group increases (on average) inversely as risk behavior. Replacing $1/r_*$ with a constant time, t_* , gives $I(t_*) \cong I_1 t_*^2$, where I_1 has yet to be determined. We approximate infection before the saturation wave began by I_0 , a small constant representing an earlier unknown growth, and obtain

$$I(t_*) = I_0 + I_1 t_*^2 \quad t_* \geq 0. \quad [4]$$

Thus, after an initial transient, HIV infection grows as the square of time.

PROGRESSION OF INFECTION TO AIDS

Given the number of individuals infected with HIV, we next estimate the resulting number of AIDS cases. The most extensive study of the progression from initial HIV infection to AIDS is given by the San Francisco Health Department

Hepatitis B Study^{†‡} and data of Lemp *et al.*[§] Define the probability of conversion to AIDS τ years after infection as $C(\tau)$. San Francisco data for the first 8 years after infection indicate that the differential probability of developing AIDS per unit time, $dC/d\tau$, is approximately zero for 2 years, followed by a 6% probability per year for the next 6 years. We assume that this 6% probability per year also applies for $\tau > 8$ years. Thus, $dC/d\tau = 0.06$ for $2 < \tau < 18$ years and is zero outside this interval. With this rate of conversion, the growth in the number of AIDS cases, dA/dt , at any given time t is the sum of the rate of newly infected cases at $t - \tau$ years, $dI(t - \tau)/dt$, multiplied by the differential probability of conversion to AIDS τ years later, $dC(\tau)/d\tau$. This sum can be written as a convolution integral over past times, τ ,

$$\frac{dA}{dt} = \int_0^{\infty} \left[\frac{dI(t - \tau)}{dt} \right] \left[\frac{dC(\tau)}{d\tau} \right] d\tau = 0.06 [I(t - 2) - I(t - 18)]. \quad [5]$$

Using I from Eq. 4 and neglecting $I(t - 18)$ because it is much smaller than $I(t - 2)$ gives

$$\frac{dA(t)}{dt} = 0.06I_1(t - 2)^2 + I_0, \quad t > 2 \text{ years}. \quad [6]$$

Integrating to obtain the cumulative number of AIDS cases, $A(t)$, gives

$$A(t) = \int_0^t [dA(\tau)/d\tau] d\tau + A_0 \\ = 0.02I_1(t - 2)^3 + 0.06I_0t + A_0, \quad t > 2. \quad [7]$$

If time is shifted back 2 years and I_0 is small, Eq. 7 has roughly the same form as Eq. 1—i.e., the cumulative number of AIDS cases grows as the cube of time. The time shift reflects the assumption that negligible AIDS cases develop during the first 2 years following HIV infection. Equating the growth factor of the cubic terms, $0.02I_1$, with the corresponding growth factor A_1 in Eq. 1 permits determination of I_1 ; or $0.02I_1 = A_1 = 174.6$ or $I_1 = 8700$. Substituting into Eq. 4 gives

$$I(t) = 8700(t + 2)^2 + I_0. \quad [8]$$

The model predicts quadratic growth of the saturation wave of infection beginning 2 years prior to the start of the cubic growth of AIDS. In other words, we have used the knowledge of the progression of the disease from infection to AIDS, $C(\tau)$, to establish both the polynomial power of time between infection and AIDS as well as the relative time scales. We have maintained our absolute time, t , as the time when the cubic term in Eq. 1 vanishes, 1981.2. Two years earlier corresponds to a zero time in the infection wave, Eq. 8, of 1979.2. For 1988.2, 9 years after the infection wave started, the number of infected is estimated by $I \approx 8700(9)^2 \approx 700,000$, where I_0 is neglected.

[†]Lemp, G. F., Barnhart, J. L., Rutherford, G. W., Piland, T. H. & Werdegard, D., Fourth International Conference on AIDS, June 1988, Stockholm, Vol. 2, p. 232, abstr. 4682.

[‡]Hessol, N. A., Rutherford, G. W., Lifson, A. R., O'Mally, P. M., Doll, L. S., Darrow, W. W., Jaffe, H. W. & Werdegard, D., Fourth International Conference on AIDS, June 1988, Stockholm, Vol. 1, p. 283, abstr. 4096.

[§]Lemp, G. F., Hessol, N. A., Rutherford, G. W., Barnhart, J. L., O'Mally, P. M., Bodecker, T., Darrow, W. W., Jaffey, H. W. & Werdegard, D., 115th Meeting of the Association of Public Health, Oct. 22, 1987, New Orleans, p. 260.

DISCUSSION

This estimate is less than the estimate of 1.5 million (18) in 1986 and is somewhat less than the current CDC estimates of 1 to 1.5 million (19). However, correcting the estimate of Eq. 8 by 10% for underreporting (19) and by 20% for the pre-1987 CDC definition leads to roughly 1 million infected in 1988.2.

So far we have assumed that growth of infection has not been affected by behavioral changes. To include this factor we must calculate when initial HIV infections occurred for the current AIDS cases and then question whether behavioral changes were significant at the time of infection. By neglecting I_0 , the most likely incubation time, \bar{t} , for the current AIDS cases can be calculated in a similar manner to Eq. 5 as $\approx t/3 + 2$ years. The mean time from infection to AIDS for AIDS cases in 1988.2 ($t = 7$) years was approximately 4.3 years, implying that for these cases the average infection occurred around 1984. Behavioral changes in homosexual men (i.e., increased condom use, etc.) began on a large scale around 1984. Therefore, a decline in the rate of growth of AIDS below the cubic rate may have already begun in homosexual men.

Eq. 4 is useful for estimating the risk behavior of those becoming infected or developing AIDS as a function of time, provided there are satisfactory estimates of the size of the "risk" population and the number of individuals infected. Consider the total number of "active" homosexuals in the principal cities. According to Kinsey *et al.* (17), we estimate this population, N , to be $\approx 10\%$ of the 40 million males of ages 20–40. If the risk behavior of these 4 million individuals is distributed according to Eqs. 2a and 2b, the size of such a cohort is $3N_0/2$, implying $N_0 = 2.7 \times 10^6$ for active homosexual males. Equating I in Eq. 3 to I in Eq. 8 and calculating the infected fraction as the ratio of homosexuals to the total cumulative AIDS cases [$\approx 65\%$ according to the CDC (1)] gives $(N_0/2)r_*^{-2} = 0.65I_1(t + 2)^2$. The risk behavior, r_* , of the homosexual group just being infected at time t is then $\approx 15/(t + 2)$. Recall that r and r_* were normalized as multiples of the average risk behavior and t is the time since 1981.2. Thus, most of the new AIDS cases, which were infected 4.3 years ago ($t = 2.7$ years), had a mean risk behavior ≈ 3 times above the average.

The model predicts that risk behavior associated with new infections is a decreasing function of time and that the earliest HIV infections occurred in persons with the highest risk behavior. This second prediction agrees with the original CDC observations (10) and the observations of others (11–14). Homogeneous mixing models do not disclose this time-dependent risk behavior for new infections, since most new infections occur in members of the average risk groups. The correlation of high average risk behavior with infection is characteristic of the early AIDS cases and emphasizes the need for including behavior in AIDS epidemic models.

We also can calculate the mean probability of transmitting infection per sexual contact, from the doubling time of the infection $[0.35(t + 2)y]$ and estimated contact frequency. This leads to typical values of the mean infectiousness per contact of 1.4×10^{-3} to 4×10^{-3} in agreement with Grant *et al.* (20). Furthermore, to sustain growth of HIV infection, each infected member of a risk group needs to infect only one new partner within the group per doubling time. Hence, the probability of infecting just one partner depends primarily on the total number of sexual contacts in the doubling time and not on the number of new partners. This assumes each individual has more than one new partner per doubling time, which is a relatively low-risk behavior.

The risk-based model explains why AIDS cases have grown polynomially and why the earlier AIDS cases were seen in high-risk-behavior individuals. However, the model does not discriminate between the two risk behaviors—new

partner rate and frequency of sexual contact. We see three possibilities for explaining why new partner rate (10–14) was the most significant risk behavior during the early epidemic: (i) frequency of sexual contact and new partner rate are closely correlated, (ii) a few individuals are highly infectious for protracted periods, and (iii) most individuals express a short period of high infectiousness followed by a long period of low infectiousness. We believe that a combination of all three possibilities contribute to the AIDS epidemic.

First, if the frequency of sexual contact is closely correlated with new partner rate, then large numbers of new partners should be associated with the earliest AIDS cases. This observation will hold regardless of whether the frequency of sexual contact or new partner rate is the most significant risk behavior for HIV infection. The distribution functions of either behavior will be similar, allowing them to be used interchangeably in the model.

Second, if a small percentage of highly infectious individuals ($i \rightarrow 1$) and a large percentage of noninfectious individuals ($i \rightarrow 0$) exist in each risk group, then new partner rate will be a significant risk behavior. Highly infectious individuals will infect virtually all their new partners and, therefore, the frequency of sexual contact will be a less significant risk behavior (21). In this case, a low average infectivity requires a small percentage of “superspreaders” in the population.

Third, if time-dependent infectivity described by Redfield *et al.* (22) is common, then new-partner rate will be a significant risk behavior. In this case, an initial short period, several weeks, of very high infectivity is followed by several years of low infectivity. As symptoms develop, infectivity again rises. If there is more than one partner during the initial period, the number of new infections will depend on partner-exchange rate.

Finally, if time-dependent infectivity is the predominant mode of HIV transmission, the early epidemic is likely to have been driven by the initial period of high infectivity. This follows because the doubling time of infection, $0.35(t + 2)$ years, is less than the prolonged period (2 years) of low infectivity (22). As the doubling time exceeds this period at $t > 3.8y$ or beginning in 1985, we anticipate an acceleration in the growth rate of HIV infections, due to increasing infectivity in the later stage of disease.^{¶¶} Changes in risk behavior could overcome this acceleration.

CONCLUSIONS

The risk-based biased-mixing model reproduces the observed cubic growth of AIDS cases when: (i) the risk behavior, r , is distributed among the population as r^{-3} ; (ii) either new-partner rate or sexual-contact frequency dominates the risk behavior, or both are closely correlated; and (iii) the cumulative probability of conversion to AIDS increases at an approximately constant rate. In addition, we find the following to be consistent with the model. (i) The total number of persons infected with HIV in 1988 was approximately 1 million based on minimal behavior changes. (ii) The mean time between infection and onset of AIDS is an increasing function of time. (iii) The decreasing growth rate of AIDS cases through 1988 was not due to changes in behavior. (iv) The mean risk behavior for HIV infection is a decreasing

function of time. (v) The mean probability of transmission per sexual contact is estimated to be 0.001 to 0.004. (vi) An increase in infectivity during the latter stages of HIV infection could increase the growth rate of AIDS; behavior modification could reduce it. (vii) New partner rate is the dominant risk factor if frequency of sexual contact and new-partner rate are strongly correlated, if a few percent of the population have a very high infectiousness, or if an initial short period of high infectiousness is followed by a prolonged period of low infectivity. Otherwise sexual contact frequency is the dominant risk behavior. (viii) Major populations, both demographic and geographic, were infected by a few high-risk individuals early in the epidemic, and only highly isolated groups may remain untouched by the epidemic.

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