Reconstruction and Future Trends of the AIDS Epidemic in the United States

RON BROOKMEYER

There has been considerable uncertainty in estimates of past and current human immunodeficiency virus (HIV) infection rates in the United States. Statistical estimates of historical infection rates can be obtained from acquired immunodeficiency syndrome (AIDS) incidence data and the incubation period. However, this approach is subject to a number of sources of uncertainty and two other approaches, epidemic models of HIV transmission and surveys of HIV prevalence, are used to corroborate and refine the statistical estimates. Analyses suggest the HIV infection rate in the United States grew rapidly in the early 1980s, peaked in the mid-1980s, and subsequently declined markedly. Due both to the decline in the underlying infection rate and to the development of effective therapies that may delay AIDS diagnosis, overall AIDS incidence may plateau during the next 5 years. However, the number of individuals with advanced HIV disease without a diagnosis of AIDS who could potentially benefit from therapy is expected to increase 40% by 1995 as infected individuals progress to more advanced stages of HIV disease. Thus, although the overall HIV infection rate has declined, the demands on the U.S. health care system for treatment and care of HIV-infected individuals remain enormous.

BY APRIL 1991, MORE THAN 170,000 INDIVIDUALS HAD been reported to the Centers for Disease Control as having AIDS. In the past decade, we have learned a great deal about the etiology and pathogenesis of HIV infection. Nevertheless, there has been considerable uncertainty about past and current HIV infection rates and future trends in AIDS incidence. Accurate estimates are important not only for developing effective strategies to prevent further spread of HIV infection, but also for assessing future demands on the health care system.

Uncertainties in past and current infection rates arise because of limited epidemiological data for monitoring the spread of HIV infection and the many assumptions underlying mathematical and statistical models. Several approaches have been used for quantifying the magnitude of the AIDS epidemic and forecasting future trends (*1*). The first approach, simple extrapolation of the AIDS incidence curve (*2*), has two serious limitations. First, the estimates depend crucially on the mathematical function used as the basis for the extrapolation, and some functions can produce anomolous results (*3*). Second, extrapolation produces projections only of AIDS cases and not HIV prevalence or incidence. Furthermore, although AIDS incidence is one of the most reliable data sources for monitoring the epidemic, it too is subject to a number of uncertainties, including delays in reporting cases, underreporting, and changes in the surveillance definition.

The second approach involves surveys of HIV prevalence. Since the development of the HIV antibody screening test, numerous HIV prevalence surveys have been conducted in special populations (*4*). Estimates of HIV prevalence based on these surveys are uncertain because of the lack of representativeness of the surveys and unknown sizes of transmission (risk) groups. Attempts to develop representative surveys, such as the National Household Seroprevalence Survey, have been stymied because of the problem of nonresponse bias (*5*).

In the third approach, principles of epidemic theory are used to develop mathematical models to describe the spread of HIV infection (*6*). This approach requires assumptions about the mixing within and between groups of individuals at risk of HIV infection, estimates of the probabilities of HIV infection per contact with an infected individual or blood product, estimates of the numbers of high-risk behaviors of an individual (for example, numbers and durations of sexual partnerships or needle-sharing behaviors among intravenous drug users) and their changes through time, the incubation period distribution, and an estimate of the initial HIV prevalence. While considerable progress has been made in the development of the propagating equations for HIV transmission models, quantitative estimates of infection rates based on this approach depend crucially on these many input parameters. Because relatively little is known about these parameters, this approach has not been useful for obtaining quantitative estimates, but does provide qualitative insight about the shape of the infection curve.

Finally in the fourth approach, popularly called back-calculation, AIDS incidence and the incubation period distribution are used to reconstruct the historical infection rates that may have occurred in order to give rise to the observed pattern of individuals diagnosed with AIDS (*7*). Uncertainties from this approach arise because of limited information about the incubation period distribution, the effects of therapy that may alter the incubation period (*8*), and errors in AIDS incidence data. Furthermore, estimates of recent infection rates are imprecise because recent infections are not yet reflected in AIDS incidence owing to the long incubation period. Nevertheless, back-calculation methods are attractive because they require few assumptions about the shape of the infection curve and require only AIDS incidence data and an estimate of the incubation period distribution.

In this article, extensions of back-calculation methods that account for changes in the incubation period due to therapies are used to produce smoothed reconstructions of historical infection rates. These rates are then propagated forward to obtain projections of AIDS incidence and numbers of individuals with advanced HIV

The author is in the Department of Biostatistics, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD 21205.

disease who have not yet progressed to AIDS. Accurate projections are important for assessing health care needs because individuals with advanced HIV disease could potentially benefit from therapy and require a different intensity of health care. Surveys of HIV prevalence and epidemic models of HIV transmission are used to assess the plausibility of the back-calculated estimates. Because the errors from back-calculation methods are distinctly different from errors from surveys and epidemic models, confidence in the estimates will increase if the various methodologies produce consistent results.

Incubation Period Distribution

The incubation period is the time between HIV infection and AIDS diagnosis. The incubation period distribution, $F(t)$, is the cumulative probability of AIDS diagnosis within t years of infection. The most reliable information on the incubation period distribution has been derived from cohort studies of HIV-infected homosexual men and hemophiliacs. Studies in which different methodologies were used have produced remarkably consistent estimates of the incubation period distribution (*9, 10*). These studies suggest that the probability of progression to AIDS within 2 years of conversion to HIV positivity is less than 0.02, rises to between 0.25 and 0.35 within 7 years and to about 0.50 within 10.0 years.

Therapies for HIV-infected individuals may lengthen the incubation period. In the middle of 1987, the Food and Drug Administration (FDA) approved zidovudine treatment for individuals with advanced HIV disease. Clinical trials among asymptomatic HIV-infected individuals (*11*) suggest that zidovudine multiplies the incidence (hazard) of progression from advanced HIV disease to AIDS by a factor of 0.35 (the treatment relative risk), although the efficacy of zidovudine may well be less outside of controlled clinical trials. Public Health Service guidelines for prophylaxis against *Pneumocystis carinii* pneumonia (for example, inhaled pentamidine) were developed by 1989. Since 1987, the incubation period could have potentially lengthened because of the composite effects of zidovudine, pentamidine, and other improvements in health care for the HIV-infected individual. However, the benefits from these therapeutic advances have not been fully realized because not all eligible infected individuals have received treatment. Studies have shown considerable variation across both transmission and demographic groups in access to treatment (*12*).

The incubation period was decomposed into a series of stages (*13*) in order to quantify changes through calendar time. It was assumed that an infected individual passes from an early stage of HIV disease (defined as $CD4^+$ cells/mm^3 > 200), to an advanced stage (defined as $CD4^+$ cells/mm^3 ≤ 200), to AIDS, and that therapy was gradually phased into the population of individuals with advanced stage HIV disease beginning in 1987. These assumptions induce changes in the incubation period distribution through calendar time (Fig. 1) (*14*). The incubation period distribution that is shown for an individual infected in 1975 or earlier refers to the natural history of HIV infection in the absence of treatment. Individuals infected increasingly later will tend to have longer incubation periods because they have an increasingly greater opportunity to have access to treatment at an earlier point in their incubation period. Similar secular changes in the incubation period have been observed directly in some epidemiological cohort studies (*15*).

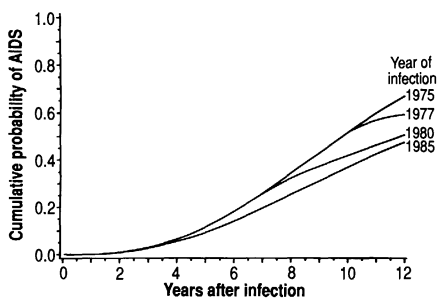

Fig. 1. Nonstationary incubation period distribution resulting from introduction of therapy into the HIV-infected population. Estimates based on a two-stage incubation period with the incubation period of the early stage modeled as a Weibull distribution (median = 6.5 years, shape parameter = 2.08) and the incubation period of the advanced stage modeled as an exponential (median = 2.5 years). Treatment phased in beginning in mid-1987 according to an exponential distribution with rate 0.20 per year for those in advanced stage disease and assumed to multiply the hazard of progression to AIDS by the factor 0.35.

Reconstruction of the AIDS Epidemic

HIV infection rates are related to AIDS incidence through the incubation period distribution. The fundamental convolution equation is given by

$$a(t) = \int_0^t I(s)F(t - s|s)ds \quad (1)$$

where $a(t)$ is the cumulative number of cases of AIDS diagnosed by year t, $I(s)$ is the infection rate in year s, and $F(t|s)$ is the incubation period distribution among individuals infected in year s.

Equation 1 is the basis for the back-calculation method that involves statistical deconvolution of AIDS incidence data. The method uses AIDS incidence data [$a(t)$], together with an estimate of the incubation period [$F(t|s)$], to glean information about past HIV infection rates [$I(s)$] through Eq. 1. The statistical solution of integral equations such as Eq. 1 arise in many different applications (*16*). Without additional structure on the shape of the infection curve, the estimates of $I(s)$ can exhibit implausible oscillations and high sensitivity to small perturbations in the data. Previous attempts to overcome these problems have used models with strong assumptions about the shape of the infection curve, (for example, logistic models) but this approach can produce severely biased infection rates, especially in the most recent past if the assumptions are incorrect (*17*). Another solution has used more flexible step functions with relatively few parameters (*7*), which yields satisfactory estimates of HIV prevalence and AIDS incidence based on simulation studies (*18*), but unsmoothed estimates of the infection curve. The method adopted here, smoothing splines, is based on Phillips-Tikhonov regularization (*19*), which yields smoothed estimates of the infection curve without invoking strong assumptions about the shape of the curve. A similar method has been employed to estimate the incubation distribution, and it was suggested that such an approach could be used to estimate the infection curve (*20*).

Individuals diagnosed with AIDS before 1 April 1990 (*21*) and the non-stationary family of incubation distributions illustrated in Fig. 1 are used in the solution of Eq. 1. Figure 2 shows the resulting reconstruction of the infection curve in the United States for the period 1978 to 1989 (*22*). The figure illustrates the rapid growth in infections during the period 1978 to 1982. The doubling times (times for the cumulative number of infections to double) increased from 7.8 months in the beginning of 1981, to 12.7 months in the beginning of 1982, to 19.2 months in the beginning of 1983. The infection rate appears to have peaked in 1984 at about 160,000 infections per year. There were marked declines in the infection rate between 1985 and 1987. As displayed in Fig. 2, the estimated infection rate after 1987 is highly uncertain, although the upper plausible range for the current infection rate is 90,000 infections per year (*23*). The cumulative number of infections from 1977 to the beginning of 1981, 1983, and 1986 were 50,000, 250,000, and 715,000 infections, respectively. The cumulative number of HIV

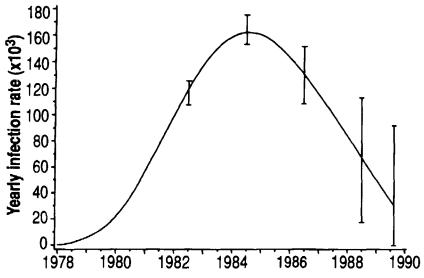

Fig. 2. Reconstruction of HIV infection rates in the United States. Estimates based on back-calculations of AIDS incidence data corrected 10% for underreporting and incubation period distribution which account for treatment effects (Fig. 1). Method based on smoothing splines (*22*) with generalized cross-validation to guide the degree of smoothing (*40*). Estimates before 1988 were not very sensitive to the degree of smoothing. Ranges account for some uncertainty in the incubation period (*23*).

infections by 1 April 1990 was 1,050,000 with a plausible range of 850,000 to 1,205,000 (*24*). An important caveat is that this range does not account for all sources of uncertainty including additional uncertainties in the incubation distribution, treatment effects, degree of smoothness, adjustments for reporting delays, and underreporting of AIDS. Because of these uncertainties, caution is especially needed with regard to the estimated time when infection rates peaked.

Similar analyses were performed for each of four transmission groups (Fig. 3). The analysis of homosexual and bisexual men shows that infection rates grew rapidly to 1982, appear to have peaked in 1984, and subsequently declined markedly. The cumulative number of HIV infections among homosexual and bisexual men was 590,000 (range 470,000 to 670,000). The epidemic among intravenous drug users grew rapidly to 1983, reached a relatively flat peak between 1984 and 1986, and appears to have declined since 1986. The cumulative number of HIV infections among intravenous drug users was 265,000 (range 200,000 to 320,000).

Infection rates among the considerably smaller subgroup of homosexuals who use intravenous drugs appear to have peaked in 1982 and dropped to low levels since 1986, perhaps due to a combination of behavioral and saturation effects. Indeed, AIDS incidence in this subgroup has been at a plateau for several years. However, the possibility that the observed plateau in this subgroup is due to a decrease in the completeness of reporting of AIDS cannot be ruled out. The cumulative number of infections among homosexuals who use intravenous drugs was 40,000 (range 30,000 to 50,000).

The heterosexual epidemic (*25*) began several years later than that in the other groups (Fig. 3). The doubling times in the beginning of 1982, 1983, and 1984 were 4.1 months, 6.4 months, and 11.5 months, respectively. Since 1986, the estimated infection rate has been 15,000 infections per year. The cumulative number of infections resulting from heterosexual transmission was 100,000 (range 75,000 to 125,000).

These estimates of the infection rates are sensitive to the incubation period distribution. Generally, an analysis in which shorter incubation periods are assumed yields lower estimates of infection rates because observed individuals with AIDS would represent a larger fraction of the cumulative number of infections (*26*). Similarly, the estimates are sensitive to the assumed treatment effects that modify the incubation period. Figure 4 shows a sensitivity analysis of the estimated cumulative HIV infections to assumptions about the treatment relative risk and the proportions of individuals with advanced stage HIV disease in treatment. For example, an analysis in which a treatment effect is not incorporated and a stable rather than a lengthening incubation period is assumed, yields a considerably smaller estimate of cumulative number of infections (715,000) and an earlier peak in the infection curve. The reason is that the falloff in the rate of growth of new individuals diagnosed with AIDS is attributed solely to significant earlier declines in infection rates rather than to a combination of both lengthening incubation periods due to treatment and declining infection rates. If the treatment effect was assumed to be more moderate (a treatment relative risk of 0.50 instead of 0.35), the estimated cumulative infections would be only 895,000 instead of 1,050,000. The estimates are also sensitive to the assumed proportions of individuals with advanced stage HIV disease who are in treatment. A smaller assumed proportion in treatment produces smaller estimates of cumulative infections. The assumptions on which Fig. 2 is based and the resulting estimates suggest that nearly 11,000 HIV-infected individuals with less than 200 $CD4^+$ cells without an AIDS diagnosis received zidovudine by 1 January 1988, which is consistent with data from drug surveillance studies (*12, 27*).

Projections of Advanced HIV Disease and AIDS Incidence

Projections of AIDS incidence can be obtained by propagating forward the infection rates in Figs. 2 and 3 and by using the incubation period distributions in Fig. 1. Because these projections do not account for the impact of future infections on AIDS incidence, various adjustments have been proposed (*28*), although they have a relatively minor effect on AIDS projections for up to 5 years because of the long incubation period. Figure 5 displays projections of AIDS incidence on a log scale and suggests that overall AIDS incidence will plateau at about 60,000 to 67,000 individuals diagnosed per year during the period 1991 to 1995 (after adjustment for 10% underreporting). Transmission group–specific projections show that AIDS incidence will also plateau among homosexual men and intravenous drug users. However, AIDS incidence among heterosexuals will more than double from 3,700 cases in 1990 to 8,700 cases in 1995.

It is possible to estimate the numbers of individuals in different stages of HIV disease by propagating forward infection rates according to stage-specific incubation distributions. Table 1 gives estimates of the numbers of infected individuals with less than 200 $CD4^+$ cells who have not yet progressed to AIDS and shows the sensitivity of the estimates to the assumed median duration of this advanced stage of HIV disease. It was estimated that at the beginning of 1989, approximately 19% of HIV-infected individuals without AIDS had less than 200 $CD4^+$ cells, which is consistent

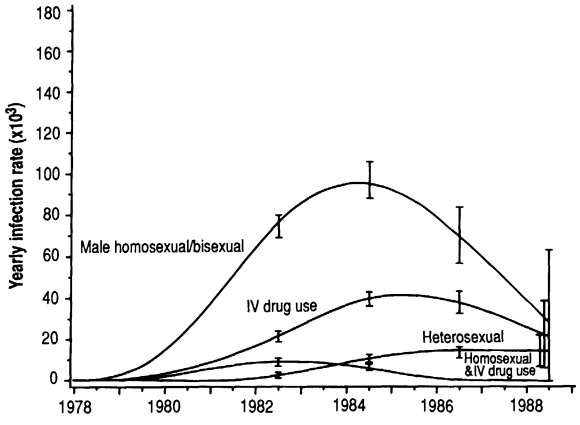

Fig. 3. Reconstruction of HIV infection rates by transmission groups. Estimates account for differences in proportions of individuals in treatment (*41*). Ranges account for some uncertainty in the incubation period (*23*). Method based on smoothing splines (*22, 40*).

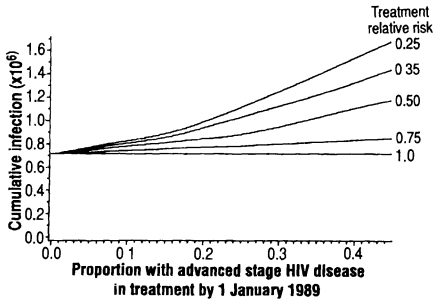

Fig. 4. Sensitivity analysis of estimated cumulative HIV infections by 1 April 1990 to assumptions about the efficacy of treatment and proportions of individuals with less than 200 $CD4^+$ cells/mm^3 and without an AIDS diagnosis who were in treatment. The effect of treatment is modeled by multiplying the hazard of progression from advanced stage HIV disease to AIDS by the treatment relative risk. Treatment phased in beginning mid-1987 among those with advanced stage HIV disease according to an exponential distribution with a yearly rate chosen to give the designated proportion in treatment by 1 January 1989.

with direct measurement of the $CD4^+$ cell distribution from epidemiologic surveys (*29*). In the beginning of 1991 there were an estimated 265,000 individuals with less than 200 $CD4^+$ cells who did not have an AIDS diagnosis, and this number can be expected to grow 40% by the beginning of 1996 (assuming that the median duration of advanced stage HIV disease is 2.5 years).

Some studies have suggested that the efficacy of zidovudine may diminish in time, perhaps due to viral drug resistance (*30*). If that is the case, AIDS incidence will increase from that shown in Fig. 5, while estimates of the numbers with advanced stage HIV disease would decrease from those shown in Table 1. For example, if the effects of zidovudine wore off after 3 years of treatment, AIDS incidence in 1995 would increase by 13%, and the number of persons without an AIDS diagnosis with less than 200 $CD4^+$ cells at the end of 1995 would decrease by 8%.

Epidemiologic Surveys

Direct measurement of HIV prevalence through epidemiologic surveys is one approach to corroborate and adjust the back-calculation estimates. For example, HIV seroconversion among active-duty military personnel can provide benchmark estimates of recent infection rates. Applying 1989 seroconversion rates among active-duty military personnel to the U.S. population (adjusted for age, race, and sex) yields an estimate of 40,000 new HIV infections occurring in 1989 (*31*). This is arguably a lower bound since the military actively discourages homosexual and intravenous drug use behavior. Back-calculations establish a plausible upper bound for the number of new HIV infections in 1989 of 90,000 infections (from Fig. 2).

Surveys and cohort studies in the San Francisco homosexual population, as well as in other cities, also provide direct estimates of infection rates. These surveys suggest that the infection rate grew rapidly between 1978 and 1981, slowed between 1981 and 1982, and subsequently declined dramatically (*4, 9, 32*). These sharp declines in infection rates among San Francisco homosexual men are corroborated by surveys that show declines both in high-risk behaviors among homosexual men and rates of rectal gonorrhea (*33*). Direct surveys suggest that infection rates among San Francisco homosexual men peaked in 1982, which is nearly 2 years earlier than the national reconstruction for the homosexual epidemic given in Fig. 3. This difference could be explained by earlier behavior changes or saturation effects (depletion of the uninfected population) in San Francisco than in the rest of the nation. In any case, both the survey data from San Francisco and the reconstruction based on back-calculations suggest that the infection rate among homosexual men peaked in 1984 or even earlier and has subsequently declined markedly.

An analysis (*31, 34*) of a large number of HIV seroprevalence surveys estimated that 1 million Americans were HIV-infected in 1989, which is consistent with the back-calculation estimates. This analysis was based on standardizing to the U.S. population, prevalence rates obtained from a number of select populations including sentinel hospital patients, general ambulatory care patients, military applicants, job corps entrants, U.S. prisoners, and childbearing women.

Table 1. Predicted prevalence of advanced stage HIV disease (less than 200 $CD4^+$ cells/mm^3 without an AIDS diagnosis), January 1991 to January 1996, and sensitivity to the incubation period.*

Year	Prevalence (in thousands) by median duration (years) of advanced stage HIV disease			Prevalence range
	1.5	2.5	3.5	
1991	158	265	366	152–380
1992	180	304	412	169–440
1993	197	333	448	182–492
1994	209	354	470	186–510
1995	216	365	480	185–524
1996	218	370	482	178–594

*Prevalence refers to numbers of individuals who are alive and with advanced stage HIV disease at each calendar time. Incubation period based on two-stage model, with the advanced stage modeled as an exponential distribution with median 1.5, 2.5, or 3.5 years and the early stage modeled as a Weibull distribution with shape parameter 2.08 and scaled so that the median of the total incubation period was fixed at approximately 10.0 years (*23*). Estimates are adjusted for an infection rate of 30,000 per year in 1990 and thereafter (based on 10,000 per year among homosexuals, intravenous drug users, and heterosexuals as suggested by Fig. 3) and ranges account for uncertainty in this rate (*39*).

Epidemic Theory Considerations

The simplest mathematical models of HIV transmission are based on the assumption that in a homogeneously mixing population, the infection rate is proportional to the product of the numbers of uninfected individuals (the susceptibles) and the numbers of infected individuals. Models of this sort predict exponential growth of infection rates in the early phase of the epidemic. Theory predicts that infection rates will subsequently slow to subexponential growth because of several phenomena. First, if there is heterogeneity in the levels of risk behavior (for example, numbers of sexual partners), the epidemic will diffuse from high- to low-risk subgroups, which causes a slowing in the growth rate (*6, 35*). Second, decreases in high-risk behavior may dampen and even reverse growth in infection rates. Third, as the epidemic matures, the susceptible population of uninfected individuals will become depleted (saturation effects) which eventually causes a peak and a subsequent downturn in infection rates.

Figure 3 shows initial exponential growth of infection rates up to 1981 among homosexual men, intravenous drug users, and homosexuals who use intravenous drugs. Since 1981, infection rates among these groups grew subexponentially, which could be explained by both reductions in levels of high-risk behaviors (for example, numbers of new sexual partners, frequency of unprotected sex, use of contaminated needles among intravenous drug users), and diffusion of the epidemic to subgroups with lower levels of high-risk behaviors. Homosexuals who use intravenous drugs are a considerably smaller risk group and the decrease in infection rates to low levels would be consistent with saturation effects.

The exponential phase of both the homosexual and intravenous drug user epidemics preceded the heterosexual epidemic by several

years. This is consistent with the fact that the primary source of infection among heterosexuals is sex with either a bisexual male or an intravenous drug user. In recent years, the infection rate among heterosexuals appears to have remained relatively constant, and models which incorporate changes in high-risk behaviors could predict similar phenomena (*1*).

Conclusions

There are sources of error associated with each of the approaches for estimating HIV prevalence (back-calculation, surveys, and epidemic models of HIV transmission), and as such, it is important to corroborate results by using the different approaches. The back-calculation methods described here are based on smoothing splines and nonstationary incubation distributions. Unlike some previous attempts at back-calculation of the AIDS epidemic in the United States, this method produces smoothed reconstructions of the infection curve while simultaneously accounting for changing incubation periods due to treatment. Epidemic models of HIV transmission can then be used to provide qualitative insight into the shape of the infection curve in order to corroborate back-calculation estimates. The relative merits of surveys versus back-calculation methods for estimating HIV prevalence depend on the transmission group under study. For example, back-calculation methods may be more reliable than surveys in both homosexual and intravenous drug using populations because of the lack of representativeness of surveys and uncertainties in the sizes of these populations. However, surveys among childbearing women may be the most useful approach for assessing the scope of the pediatric epidemic.

It is considerably more difficult to estimate current and future incidence of HIV infection than it is to estimate either HIV prevalence or project short-term AIDS incidence. Back-calculation methods and single cross-sectional surveys of HIV prevalence provide little information about recent infection rates, and no information about future infection rates. Although epidemic models of HIV transmission may be useful for evaluating the relative effects of different intervention programs (*36*), quantitative estimates of future infection rates from this approach must be interpreted cautiously because of uncertainties in the many input parameters. Surveillance for incident HIV infection in representative cohorts of various population segments is one useful means for monitoring infection rates (*37*). Serial cross-sectional surveys may also be useful for monitoring infection rates; however, the interpretation of data from such surveys is somewhat problematic because the surveyed population is constantly changing (*38*).

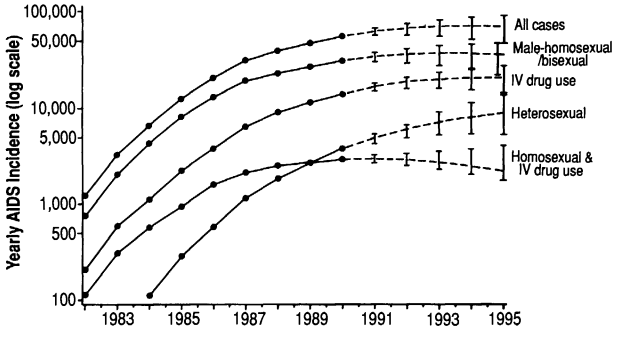

Fig. 5. Projections of annual AIDS incidence 1991 to 1995 (log scale) for the entire United States and four transmission groups. Projections corrected 10% for underreporting. Infections after April 1990 are assumed to occur at rate 10,000 per year among homosexuals, intravenous drug users, and heterosexuals, and 30,000 per year overall. Ranges account for uncertainty in this infection rate (*39*) and some uncertainty in the incubation period (*23*).

The results described here suggest that the overall HIV infection rate in the United States has declined dramatically since its peak in the 1980s. However, there is very limited data to determine whether this trend of declining infection rates is still continuing, nor can the possibility of a future "second wave" epidemic in some population subgroups be ruled out. These analyses suggest that AIDS incidence may plateau during the next 5 years. This plateau is due not only to an earlier decline in the underlying infection rate, but also to therapies that may delay AIDS diagnosis. However, the number of individuals with advanced stage HIV disease but without a diagnosis of AIDS will grow by 40% during the next 5 years. In 1989, the Public Health Service recommended zidovudine therapy for asymptomatic infected individuals with less than 500 $CD4^+$ cells/mm^3. Future therapeutic advances may involve even earlier treatment interventions and thus increase the numbers of individuals who could potentially benefit from treatment. Future demands on the health care system for the treatment and care of HIV-infected individuals thus remain enormous.

REFERENCES AND NOTES

1. M. H. Gail and R. Brookmeyer, *J. Natl. Cancer Inst.* **800**, 900 (1988).
2. J. W. Curran *et al.*, *Science* **229**, 1352 (1985).
3. M. H. Gail and R. Brookmeyer, *J. Am. Med. Assoc.* **263**, 1538 (1990).
4. Centers for Disease Control, *Morb. Mortal. Wkly. Rep.* **36**, (1987), suppl. S-6.
5. Centers for Disease Control, *ibid.* **40**, 1 (1991).
6. R. M. May and R. M. Anderson, *Nature* **326**, 137 (1987).
7. R. Brookmeyer and M. H. Gail, *Lancet* **ii**, 1320 (1986); *J. Am. Stat. Assoc.* **83**, 301 (1988).
8. M. H. Gail, P. S. Rosenberg, J. J. Goedert, *J. AIDS* **3**, 296 (1990).
9. P. Bacchetti and A. R. Moss, *Nature* **338**, 251 (1989).
10. R. Brookmeyer and J. J. Goedert, *Biometrics* **45**, 325 (1989); N. A. Hessol *et al.*, *Am. J. Epidemiol.* **130**, 1167 (1989); J. Taylor, J. Kuo, R. Detels, *J. AIDS* **4**, 69 (1991).
11. P. Volberding *et al.*, *N. Engl. J. Med.* **322**, 941 (1990).
12. P. S. Rosenberg *et al.*, *J. AIDS* **4**, 392 (1991); R. Moore, J. Hidalgo, B. Sugland, R. Chaisson, *N. Engl. J. Med.* **324**, 1412 (1991); N. Graham *et al.*, *J. AIDS* **4**, 267 (1991).
13. I. Longini *et al.*, *Stat. Med.* **8**, 831 (1989); I. Longini, *J. AIDS* **3**, 930 (1990).
14. R. Brookmeyer and J. Liao, *Biometrics* **46**, 1151 (1990).
15. M. T. Schecter *et al.*, *Lancet* **i**, 1026 (1989).
16. F. O'Sullivan, *Stat. Sci.* **1**, 502 (1986).
17. N. E. Day, S. M. Gore, M. A. McGee, M. South, *Philos. Trans. R. Soc. London Ser. B* **325**, 123 (1989); V. DeGruttola and S. Lagakos, *Stat. Med.* **8**, 35 (1989).
18. P. S. Rosenberg, M. H. Gail, D. Pee, *Stat. Med.*, in press.
19. D. Phillips, *J. Assoc. Comput. Mach.* **9**, 84 (1962); A. Tikhonov, *Sov. Math.* **5**, 1035 (1963).
20. P. Bacchetti, *J. Am. Stat. Assoc.* **85**, 1001 (1990); for a related approach, see J. Taylor, J. Kuo, R. Detels [*J. AIDS* **4**, 69 (1991)]. An alternative smoothing algorithm is given in N. G. Becker, L. Watson, J. Carlin (*Stat. Med.*, in press).
21. AIDS incidence data based on cases reported by September 1990 was provided by T. Green and J. Karon of CDC and was adjusted for delays in reporting and inflated 10% for underreporting [A. Hardy, *Publ. Health Rep.* **102**, 386 (1987)]. Recent cases with no identified risk group were redistributed according to historical trends.
22. The period January 1977 to April 1990 was grouped into 12 time intervals (the lengths of the first and last intervals were 2 and 1.25 years, respectively; all other intervals were yearly), and infections were assumed to occur according to Poisson process in each interval with intensity β_j. Estimates of infection rates were obtained by minimizing the sum of a term that measures the closeness of the data to the model [$\Sigma\ (y_i - \hat{y}_i)^2/\hat{y}_i$, where y_i and $\hat{y}_i$ are observed and predicted quarterly AIDS incidence, respectively], and a term that measures smoothness of the infection curve [a discrete approximation to the integrated squared second derivative of the infection curve and for intervals of equal length w, this is $\lambda\Sigma(\beta_{j+2} - 2\beta_{j+1} + \beta_j)^2/w^3$, where λ is the smoothing parameter]. Estimates were obtained through iteratively reweighted least squares.
23. All cited ranges are based on 95% confidence limits (conditional on the degree of smoothness) under three different incubation distributions (see Table 1 note). The ranges are the maximum of the three upper and minimum of the three lower confidence limits computed from the three incubation distributions. The hazard of AIDS for these three distributions rises rapidly with time from infection and eventually levels off. The three distributions account for some uncertainty in how quickly the hazard levels. The ranges account for extra-Poisson variation with overdispersion parameter estimated by $\Sigma_{i=1}^{n}\ (y_i - \hat{y}_i)^2/\gamma_i(N\text{-trace H})$, where H is the smoothing spline hat matrix satisfying $\hat{y} = Hy$.
24. The analyses were based on all cases of AIDS without adjustments for the change in the AIDS surveillance definition in 1987. When the analysis is restricted to a consistently defined series [individuals who meet the pre-1987 criteria with presumptive diagnosis included; see J. Karon, T. Dondero, J. Curran, *J. AIDS* **1**, 542 (1988)], the estimated cumulative number of infections decreased by 16%.

These estimates are consistent with earlier back-calculation estimates based on AIDS incidence data through mid-1987 [see P. S. Rosenberg, R. J. Biggar, J. J. Goedert, M. H. Gail, *Am. J. Epidemiol.* **133**, 276 (1991)].
25. The analysis of the heterosexual transmission group excludes individuals born in pattern II countries, defined as areas of central, eastern, and southern Africa and some Caribbean countries [Centers for Disease Control, *Morb. Mortal. Wkly. Rept.* **37**, 294 (1988)].
26. The infection rate estimates are sensitive to both the location and shape of the incubation period distribution. For example, if the stage-specific hazards are scaled so that the median incubation period is 9 years instead of 10 years, the estimated cumulative number of infections is 15% lower, although the shape of the infection curve is similar to Fig. 2. See also P. S. Rosenberg and M. H. Gail, *Ann. Epidemiol.* **1**, 105 (1990); J. Taylor, *Stat. Med.* **8**, 45 (1989); J. Hyman and E. Stanley, *Math. Biosci.* **90**, 415 (1988).
27. The back-calculation results on which Fig. 2 is based suggest that 110,000 individuals had fewer than 200 $CD4^+$ cells and did not have an AIDS diagnosis on 1 July 1987. If it is assumed that 20% of these eligible patients enter treatment each year beginning 1 July 1987, then about 11,000 were in treatment in the beginning of 1988. For estimates from drug surveillance studies, see E. Andrews, T. Creagh-Kirk, K. Pattishell, H. Tilson, *J. AIDS* **3**, 460 (1990).
28. R. Brookmeyer and A. Damiano, *Stat. Med.* **8**, 23 (1989); P. S. Rosenberg and M. H. Gail, *Appl. Stat.* **40**, 269 (1991).
29. J. F. Brundage *et al.*, *J. AIDS* **3**, 92 (1990).
30. B. A. Larder, G. Darby, D. D. Richman, *Science* **243**, 1731 (1989).
31. Centers for Disease Control, *Morb. Mortal. Wkly. Rept.* **39** (no. 7), 112 (1990).
32. M. Segal and P. Bacchetti, *J. AIDS* **3**, 832 (1990).
33. L. McKusick, W. Horstman, T. Coates, *Am. J. Publ. Health* **75**, 493 (1987); J. Pickering *et al.*, *Math. Model.* **7**, 661 (1986).
34. T. J. Dondero, M. St. Louis, J. Anderson, L. Petersen, M. Pappaiognou, paper presented at the Fifth International Conference on AIDS, Montreal, 4 to 9 June 1989 (International Development Research Centre, Ottawa, 1989), abstract, p. 45
35. H. W. Hethcote and J. A. Yorke, *Gonorrhea Transmission Dynamics and Control* (Springer-Verlag, Heidelberg, 1984).
36. M. H. Gail, D. Preston, S. Piantadosi, *Stat. Med.* **8**, 59 (1989).
37. J. G. McNeil *et al.*, *N. Engl. J. Med.* **320**, 1581 (1989).
38. J. F. Brundage *et al.*, *J. AIDS* **3**, 1168 (1990).
39. Ranges for projected AIDS incidence account for future infection rates as high as 90,000 per year for all cases; 30,000 per year for each of the following groups: homosexuals, intravenous drug users, and heterosexuals; and 10,000 per year for homosexuals who use intravenous drugs. All lower ranges account for infection rates as low as 0 per year.
40. F. O'Sullivan, B. S. Yandell, W. J. Raynor, *J. Am. Stat. Assoc.* **81**, 96 (1986). Smoothing parameter in Fig. 2 was 6.25×10^{-8}. Smoothing parameters in Fig. 3 for homosexuals, intravenous drug users, homosexuals who use intravenous drugs and heterosexuals were 1.25×10^{-7}, 1.75×10^{-7}, 2.0×10^{-7}, and 1.0×10^{-7}, respectively.
41. Treatment use phased in according to an exponential distribution; among homosexuals, beginning in mid-1987 at a rate of 0.3/year; among intravenous drug users and heterosexuals, beginning in 1988 at a rate of 0.05 per year; among homosexuals who use intravenous drugs, beginning in 1988 at a rate of 0.1 per year. Rates suggested by drug surveillance studies (*12*).
42. The author gratefully acknowledges many helpful discussions with R. Fox, J. Curran, M. H. Gail, T. Green, J. Karon, J. Liao, P. S. Rosenberg, and S. Zeger; P. Hubbard for manuscript preparation, and the support of PHS grant CA-48723 awarded by the National Cancer Institute.

Celestial Mechanics on a Microscopic Scale

T. UZER, DAVID FARRELLY,* JOHN A. MILLIGAN,* PAUL E. RAINES, JOEL P. SKELTON

Classical and semiclassical methods are unrivaled in providing an intuitive and computationally tractable approach to the study of atomic, molecular, and nuclear dynamics. An important advantage of such methods is their ability to uncover in a single picture underlying structures that may be hard to extract from the profusion of data supplied by detailed quantum calculations. Modern trends in semiclassical mechanics are described, particularly the combination of group theoretical methods with techniques of nonlinear dynamics. Application is made to intramolecular energy transfer and to the electronic structure of atomic Rydberg states in external electric and magnetic fields.

THE POPULAR IMAGE OF THE ATOM AS A MINIATURE SOLAR system stems from the experiments of Rutherford and the old quantum theory of Niels Bohr. This theory is described in Max Born's book *Mechanics of the Atom* and is based on the assumption that the laws of classical mechanics apply equally to electrons and planets (*1, 2*). Within months of the appearance of Born's book in 1925, however, a dramatic revolution in physics occurred and the old quantum theory was ousted by the new quantum mechanics of Schrödinger and Heisenberg. As a result, attention in atomic and molecular physics shifted away from classical mechanics, which was thought by many to be a complete and closed field. The analogy between the structure of the atom and that of the solar system seemed invalid, and classical mechanics became the domain of the astronomer. However, new developments within the last two decades have spurred a remarkable revival of interest in classical mechanics (*3*). The implications extend well beyond astronomy, and much present-day research in classical mechanics is being performed in the context of microscopic dynamics. This confluence of interests between atomic and molecular physicists and astronomers is proving beneficial to the study of both classical and quantum systems, as will be illustrated in this article.

The fundamental connection between classical and quantum mechanics has fascinated physicists ever since the discovery of quantum theory (*3–6*), with the most interesting questions relating to the regime where quantum and classical behavior start to overlap. Classical mechanics is an asymptotic limit of quantum mechanics valid when Planck's constant h is small in comparison to relevant system parameters. Although quantum mechanics provides a correct description of nature, it does not hold the intuitive appeal of classical theories, which are also easier to implement: the challenge, therefore, is to understand when the asymptotic classical behavior sets in. Unexpectedly, classical methods many times work rather well in regimes that appear to be removed from the formal asymptotic limit; it is apparent that the uncertainty principle has vanishing impact on the dynamics of a galaxy, but it might seem surprising that interesting behavior of quantum systems can often be described with the use of classical methods. Much of the analysis in molecular vibrational and rotational spectroscopy, for example, is performed using an essentially classical normal mode analysis, which provides a good picture of the dynamics (*7*).

T. Uzer, P. E. Raines, and J. P. Skelton are in the School of Physics, Georgia Institute of Technology, Atlanta, GA 30332. D. Farrelly and J. A. Milligan are in the Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90024.

*Present address: Department of Chemistry and Biochemistry, Utah State University, Logan, UT 84322.