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FOREWORD

We know that AIDS is the final stage of HIV infection (the Human Immuno-Deficiency Virus), and that HIV is identifiable in infected individuals from within a few weeks of infection. For no large national or other unselected population do we have statistics of HIV. The only reasonably trustworthy information is the number of cases diagnosed as AIDS. The statistical problem is to track back to the number of HIV infections, given some general information on the speed at which the disease progresses from initial infection to full-blown AIDS.

Professor Artzrouni and Dr. Heilig have made effective use of the known sequence, plus data on AIDS cases by risk groups, to estimate HIV infections for five European countries, which is almost equivalent to estimating future AIDS cases and deaths. At one time it was feared that AIDS might wipe out whole populations, that it even threatened the human race. We now know that behavior is such as to safeguard the race against any such ultimate danger. The population at risk is only a small fraction of the national total, perhaps of the order of one one-thousandth.

A logistic curve increases in proportion to the number of AIDS cases and also in proportion to the number of susceptibles that are not yet infected. Thus its fitting permits an estimate of the number of infected in the population, and of the time when the annual incidence of AIDS cases will reach its maximum. Artzrouni and Heilig estimate that point of time to be the early to mid 1990s. According to the nature of the logistic, half of those who will ultimately contract AIDS will then have contracted it; the number of future cases will be no more than the number already infected.

Of course, this result is based on behavior in the five European countries and risk-groups concerned; it cannot be applied to countries where sexual and other culture is grossly different.

Nathan Keyfitz
Leader, Population Program

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ABSTRACT

Projections of the spread of the acquired immunodeficiency syndrome (AIDS) and of its etiologic agent, the human immunodeficiency virus (HIV), are presented for homosexual/bisexual men and intravenous drug users in the five European countries with the largest caseloads. The results suggest that the HIV epidemic for French, German, and British homosexual/bisexual men has peaked around 1985 and declined rapidly thereafter. By the end of the century, and for a median incubation period m of AIDS equal to 8 years, the total numbers infected in these groups are predicted to be about 31,000, 15,000, and 9,000, respectively. (These estimates more than double if m is taken equal to 12 years). The results suggest that the HIV epidemic among Italian and Spanish intravenous drug users (IVDUs) peaked in 1986 and also decreased rapidly thereafter. For an assumed median incubation period m of 8 years, the total number of infected IVDUs by the end of the century is predicted to be about 22,000 and 16,000 in Italy and Spain, respectively. (Again, these estimates more than double if m is taken equal to 12 years.) The projections suggest that in the late 1980s or early 1990s the annual incidence of AIDS cases among IVDUs in Spain and Italy will overtake the incidences of homosexual/bisexual AIDS cases in the Federal Republic of Germany and the United Kingdom. In all cases the annual incidence of AIDS will reach its maximum in the early to mid 1990s. However, the AIDS epidemic will be protracted because of the long incubation period.

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Projections of the HIV/AIDS Epidemic for Homosexual/Bisexual Men and Intravenous Drug Users in Five European Countries

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INTRODUCTION

By June 1989 the WHO Collaborating Centre on AIDS in Paris had received 24,894 reports of AIDS cases from 32 European countries (WHO Collaborating Center on AIDS, 1989). This continued increase in the number of AIDS cases in Europe testifies to the need for intensified efforts at ascertaining the future spread of the human immunodeficiency virus (HIV), the etiologic agent of AIDS. Indeed, public health authorities need accurate projections of the HIV/AIDS epidemic in order to plan future AIDS-related health care services (Brandt, 1989). To date, three approaches have been used to project the epidemic.

First, one can extrapolate current AIDS incidence data using various statistical procedures. One such method hinges on the assumption that the doubling time of the number of AIDS cases will remain constant in the short-run (Downs *et al.*, 1987). The U.S. Public Health Service, on the other hand, has fitted a quadratic polynomial to a power transformation of the AIDS incidence to obtain projections of AIDS cases in the United States through 1992 (Karon *et al.*, 1988). Although useful for short-term projections, these purely statistical methods do not take into account the transmission dynamics of HIV and do not provide information on the natural history of HIV.

Second, micro-level models of the transmission dynamics of HIV can be developed with a view toward projections. These models are "behavior-dependent" and hinge on transmission rates of the virus between individuals and between risk groups. This makes their implementation difficult because often very little is kown on the behavioral components and the parameters of the models, e.g., rate of partner change for homosexuals or rate of needle sharing for intravenous drug users (IVDUs) (Anderson *et al.,* 1986; May and Anderson, 1987; Dietz, 1988; Anderson and May, 1988; Anderson, 1988a; Blythe and Anderson, 1988a, 1988b, 1988c; Hyman and Stanley, 1988; Nahmias, 1989; De Gruttola and Lange, 1989; Bailey, 1988; Castillo-Chavez *et al.*, 1989; Longini *et al.*, 1989; Bongaarts, 1989; Tan, 1989). Reviews can be found in Anderson, (1988b), and Isham, (1988). Micro-models that emphasize the sexual behavior of the at-risk population were proposed by Abramson (1988), Abramson and Rothschild (1988), and Blythe (1989) among others. Several computer models simulate the dynamics of HIV/AIDS in specific risk groups or areas (Hethcote, 1989; Cooley *et al.*, 1989; Ahlgren *et al.*, 1989; Stigum *et al.*, 1989; Bolz *et al.*, 1989; Stanley *et al.*, 1989; Siegel *et al.*, 1989; van Druten *et al.*, 1989).

A third set of methods builds upon the long and variable incubation period that separates infection with HIV and onset of AIDS. These methods have in common the implicit or explicit reconstruction ("back-calculation") of the number of persons infected in the past on the basis of the observed number of AIDS cases and for a given incubation period distribution. One such method is based on a parametrization of the epidemic density I(s) and on the assumption that the distribution of AIDS cases is multinomial. (Brookmeyer and Gail, 1986, 1987, 1988; Brookmeyer and Damiano, 1989; Taylor, 1989). A predicted number of AIDS cases is obtained by projecting forward the past number of infected individuals.

A somewhat different approach to the same problem relies on non-linear regression methods to fit a modeled HIV epidemic curve to the observed AIDS incidence data. The parameters of the HIV epidemic curve are chosen in such a way that the resulting predicted AIDS epidemic approximates as closely as possible the observed epidemic. If appropriately chosen, the modeled HIV epidemic can then be extrapolated and therefore yield projections of the AIDS epidemic.

This approach will be used here to reconstruct then extrapolate the HIV epidemic among the largest risk groups in five European countries (i.e., homosexual/bisexual men in France, the Federal Republic of Germany, and the United Kingdom; and intravenous drug users (IVDUs) in Italy and Spain. The logistic growth curve will be the functional form for the cumulative number of HIV-infectives. After extrapolation, the logistic will yield a projected AIDS epidemic, complete with confidence intervals. A sensitivity analysis will show that the accuracy of the projections depends, among other things, on a correct specification of the incubation period distribution. Finally, the pitfalls, sources of errors and other problems will be discussed.

THE MODEL

A logistic modeling of the spread of HIV was proposed in the context of an important study of transient effects in the AIDS epidemic (Gonzalez and Koch, 1987). The logistic is a symmetric S-shaped curve that captures the dynamics of a homogeneous epidemic that grows at first exponentially, then linearly, and then levels off when the pool of susceptibles is depleted or when prophylactic measures or changes in behavior slow down the spread of the virus. One form of the logistic curve for the cumulative number H(t) of HIV infections at time t is

$$H(t) = \frac{A}{1 + B\exp(-rt)} \tag{1}$$

where r is the initial growth rate of the spread of HIV and A is the total number of infected persons.

In a discrete formulation the annual number of new infections h(t) is h(t)=H(t)-H(t-1) = number of new infections in the interval (t-1, t).

The number a(t) of new AIDS cases in the interval (t-1,t) is thus of the form

$$a(t) = \sum_{1=1}^{30} h(t-i)p(i) = \sum_{1=1}^{30} [H(t-i)-H(t-i-1)]p(i) + \varepsilon(t) \tag{2}$$

where p(i) is the probability density function of the incubation period. (The maximum possible incubation period is 30 years); $\varepsilon(t)$ is the error term in the time series {a(t)}, which is therefore modeled as the sum of a deterministic component (depending on A, B,r,t and {p(i)}) and of the error term $\varepsilon(t)$. Eq. (2) is the discrete version of the well-known integral equation relating the density of new AIDS cases to the density of new HIV cases.

The density function p(x) is taken from the Weibull family of curves and is thus of the form $p(x) = \beta\alpha^{-\beta} x^{\beta-1} \exp(-[x/\alpha]^{\beta})$ where β is the shape parameter and α the scale parameter which is equal to $m/(\ln 2)^{1/\beta}$ (m is the median incubation period). The shape parameter β is taken equal to 2.571, a value obtained on the basis of a study of homosexual/bisexual men in San Francisco (Lui *et al.*, 1988). The scale parameter α determines the median (or the mean) value of the incubation period. It is currently believed that the mean is about 8 years (Lui *et al.*, 1988). However, estimates of the mean have lengthened with time as more data have become available, and the possibility of a longer mean incubation period cannot be ruled out. We will use here the median rather than the mean value of the incubation period and perform the analysis for a "most likely" median m of 8 years, and a "less likely" (but still plausible) median of 12 years. The Weibull curve for m=8 years is given in Figure 1.

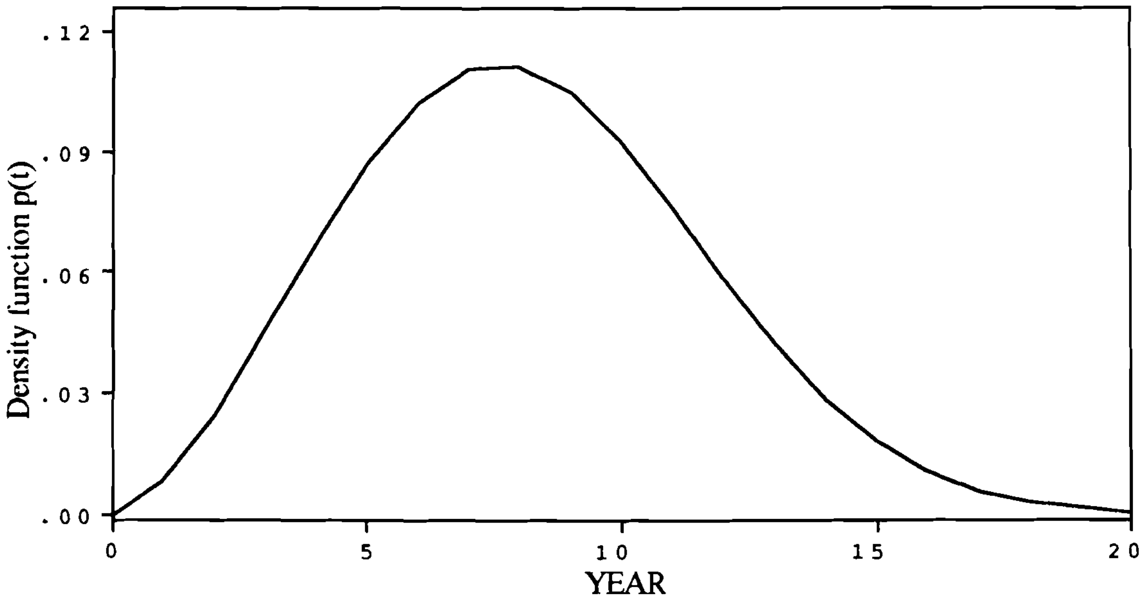

Figure 1. Weibull density function with median 8 years and shape parameter 2.571.

Rewriting Eq. (2) in terms of the logistic equation (1) yields

$$a(t) = \sum_{i=1}^{30} \left[\frac{A}{1 + B\exp(-r[t-i])} + \frac{A}{1 + B\exp(-r[t-i-1])} \right] p(i) \; + \varepsilon(t) \qquad (3)$$

For simplicity we let G(A, B, r, p(u), t) be the deterministic component of the time series a(t) in Eq. (3) (i.e., $a(t) = G(A, B, r, p(u), t) + \varepsilon(t)$). The error terms will be assumed to be independently distributed with mean 0 and variance proportional to $G^2(A, B, r, p(u), t)$, i.e., $Var(\varepsilon(t)) = \sigma^2 G^2 (A, B, r, p(u), t)$ for some σ^2. This implies that the fractional terms $F(t) = [a(t) - G(A, B, r, p(u), t)]/ G(A, B, r, p(u), t)$ (i.e., the percentage deviations between observed and expected values of a(t)) will be independently and identically distributed normal variables with mean 0 and variance σ^2.

The fractional squares FS(t) are defined as $F(t)^2$, and the parameters A, B, r are estimated by minimizing the sum of fractional squares $SFS = \Sigma\, FS(t)$. The predicted number of AIDS cases at a future time t is then $\hat{a}(t) = G(\mathbf{A}, \mathbf{B}, \mathbf{r}, p(u), t)$ where **A, B, r** are the estimated values of A, B, r. An estimate s^2 of σ^2 is obtained as the ordinary estimate of the variance of the fractional terms F(t) where A, B, r are replaced by their estimated values **A, B, r**. An empirically based 95% percent confidence interval for a predicted value $\hat{a}(t)$ is then

[G(**A**, **B**, r, p(u), t)(1 - t_{n-1} s); G(**A**, **B**, r, p(u), t)(1 + t_{n-1} s)] (Gilchrist, 1976). Confidence intervals for the cumulative incidences of AIDS are obtained after noting that the variance of a sum of independent normal variables is the sum of the variances.

RESULTS

The results are summarized in Table 1, with more detailed yearly results in Tables 2A-2E for the five countries when the median incubation period m is 8 years. The beginning of the HIV epidemic among homosexual/bisexual men was set in 1976. Because the epidemic has started later among IVDUs, the first year of the epidemic for IVDUs was taken as 1978.

The results for the Federal Republic of Germany are graphically represented in Figures 2a (for m=8 years) and 2b (for m=12 years). (Note the different scales for the two figures.) The graphs for the other countries are similar.

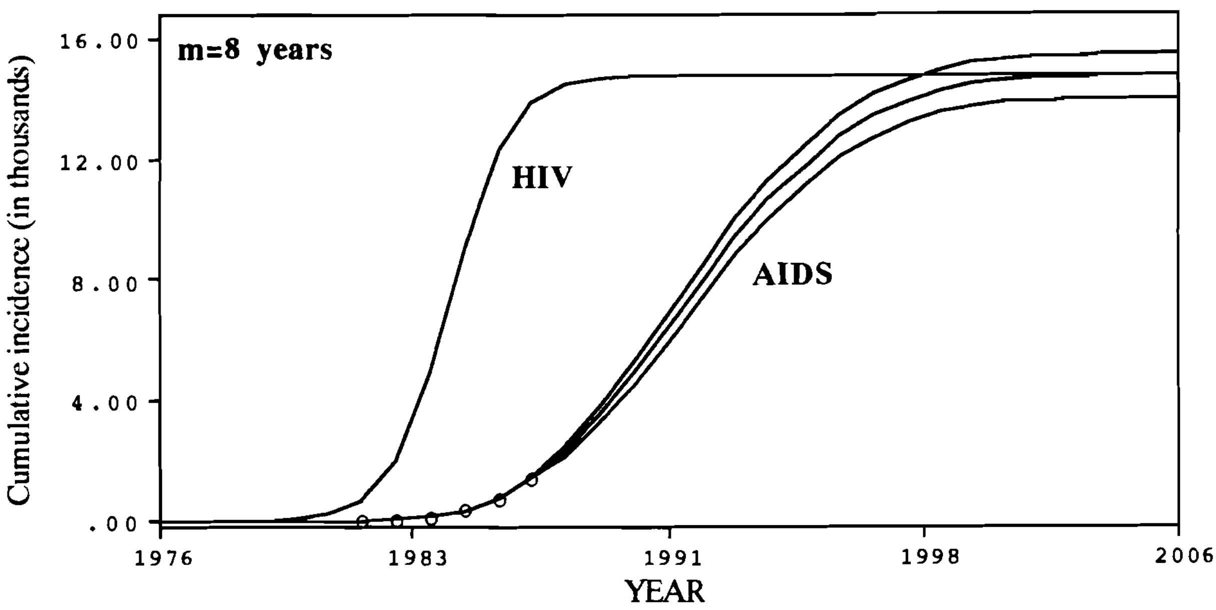

Figure 2a. Reconstructed logistic HIV epidemic and predicted AIDS epidemic (with 95% confidence interval) that best approximates the observed incidence (circles) of AIDS for homosexual/bisexual men in the Federal Republic of Germany. m=8 years.

The reconstructed cumulative incidence of HIV infection is plotted, together with the corresponding AIDS epidemic and the 95% confidence interval. It was not possible to obtain confidence intervals for the incidence of HIV infection because there is no observable error structure for the HIV epidemic.

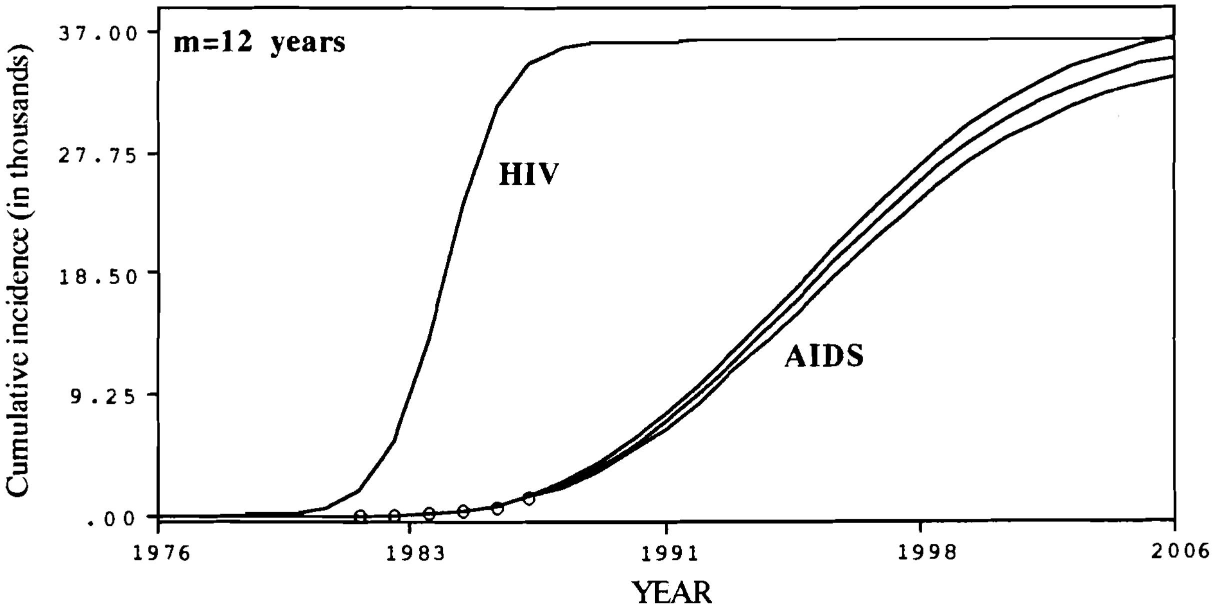

Figure 2b. Reconstructed logistic HIV epidemic and predicted AIDS epidemic (with 95% confidence interval) that best approximates the observed incidence (circles) of AIDS for homosexual/bisexual men in the Federal Republic of Germany. m=12 years.

The graphs show that by the end of the century the predicted AIDS epidemic (middle AIDS curve) approaches the cumulative incidence of HIV infection. This reflects the assumption that all infected persons will eventually develop AIDS. The convergence of the HIV curve and of the middle AIDS curve is particularly obvious in Figure 2a, when m=8 years. For m=12 years, the epidemic is more protracted, and the number of AIDS cases by the end of the century has not yet reached the total number of infected persons, even though HIV had stopped spreading about 15 years earlier.

In all cases the logistically reconstructed HIV epidemic grows rapidly at the beginning, reaches its maximum in eight to twelve years, then decreases rapidly thereafter. In France, the Federal Republic of Germany, and the United Kingdom ("western countries") the number of newly infected homosexual/bisexual men reaches its maximum between 1984 and 1986, depending on the country and on the assumed median incubation period. For IVDUs in Spain and Italy ("southern countries") this maximum is always in 1986.

With a median incubation period of 8 years the total numbers of homosexual/bisexual men predicted to be infected by the end of the century in France, the Federal Republic of Germany, and the United Kingdom are about 31,000, 15,000, and 9,000 respectively. These estimates more than double if m=12 years. This sensitivity to m is not surprising. Indeed, if m is larger, the probability of coming down with AIDS at the early stages of the infection is smaller and therefore a larger number of HIV-infectives will be "reconstructed" at the beginning of the epidemic in order for these infectives to "generate" the observed cases of AIDS.

With m=8 years the model predicts there will be 22,000 Italian and 16,000 Spanish infected IVDUs by the end of the century. Again, these estimates more than double if m=12 years.

The cumulative incidences of AIDS in 2000 are of course also sensitive to the median incubation period. For example, in France a 95% confidence interval for the cumulative number of AIDS cases in 2000 is [29,734-30,724] if m=8 years; these lower and upper limits are multiplied by two if m=12 years. Similar results for the other countries (Table 1).

Growth patterns

The sensitivity of the total numbers infected is counter-balanced by a robustness of the *growth patterns*. As indicated above, in the three western countries and for both values of the median incubation period the logistically modeled HIV epidemic peaks between 1984 and 1986. This peak is reached in 1986 for the IVDUs of southern Europe, regardless of the incubation period.

If the median incubation period m is 8 years, the resulting AIDS epidemics reach their maximum 6 or 7 years after the maximum of HIV. The AIDS epidemic among homosexual/bisexual men in the three western countries reach their maximum in 1991 or 1992. In the United Kingdom this maximum is in 1991 with 984 cases (95% confidence interval=[808-1,159]). In France and the Federal Republic of Germany the maximum is in 1992 with 3,187 cases (95% confidence interval=2,997-3,377]) and 1,521 cases (95% confidence interval=1,242-1,800]), respectively. When m=8 years the maximum annual incidence of AIDS in Spain is reached in 1993 and is 1,725 (95% confidence interval= [1,578-1,872]); in Italy this maximum is reached in 1992 and is 2,425 (95% confidence interval= [1,976-2,884]). If m=12 years then in the Federal Republic of Germany and in Spain the maximum annual incidence of AIDS occurs three years later than it would have if m=8 years; for all other countries the maximum occurs four years later (see Table 1).

These results show that a longer incubation period does not change the timing of the maximum of the HIV epidemic but does result in a reconstructed HIV epidemic that is much larger and more protracted (see Figures 2a, 2b).

Country	Tot. HIV incidence	Max. annual HIV incidence (& year)	Max. annual AIDS incidence (95% conf. int.); year	95% conf. int. for cumul. AIDS cases in 2000	R^2	Doubling time t_d
France (HBs)						
m=8 years	31,012	8,003 (86)	3,187 (2,997-3,377); 92	29,734-30,724	0.9993	7
m=12 years	79,183	20,390 (85)	5,682 (5,315-6,049); 96	59,010-61,155	0.9987	7
FRG (HBs)						
m=8 years	14,731	4,158 (85)	1,521 (1,242-1,800); 92	13,728-15,173	0.9971	7
m=12 years	36,266	10,388 (85)	2,604 (2,135-3,073); 95	27,125-29,906	0.9978	7
UK (HBs)						
m=8 years	9,263	2,953 (84)	984 (808-1,159); 91	8,720-9,603	0.9957	6
m=12 years	23,907	7,802 (84)	1,742 (1,406-2,077); 95	18,503-20,505	0.9924	6
Italy (IVDUs)						
m=8 years	22,421	10,897 (86)	2,425 (1,967-2,884); 92	20,722-23,090	0.9928	4
m=12 years	62,164	30,075 (86)	4,579 (3,734-5,425); 96	43,819-48,676	0.9945	4
Spain (IVDUs)						
m=8 years	16,107	6,695 (86)	1,725 (1,578-1,872); 93	15,329-16,090	0.9992	5
m=12 years	43,553	18,032 (86)	3,192 (2,929-3,456); 96	31,567-33,083	0.9995	5

Table 1. Summary results of reconstructed and projected HIV/AIDS epidemic among homosexual/bisexual (HB) men in France, the Federal Republic of Germany, the United Kingdom and among IVDUs in Italy and Spain. The total HIV incidence is the estimated value of A (see Eq. (1)); the doubling time t_d is 12ln(2) divided by the estimated value of the growth rate r.

TABLE 2A

Reconstructed and projected logistic HIV epidemic curve (with predicted AIDS epidemic) that yields the best fitting AIDS epidemic curve for homosexual/bisexual men in France (1982-1987); m=8 years.

Source of AIDS incidence data: WHO Collaborating Centre on AIDS (Paris). Data are corrected for reporting delays by authors.

Year	HIV		AIDS			
	Annual Expec.	Cumul. Expec.	Annual Obs.	Annual Expec.	Annual 95% Conf. Int.	Cumul. 95% Conf. Int.
1976	1	1		0		
1977	2	4		0		
1978	8	11		0		
1979	23	34		1		
1980	71	106		2		
1981	218	324		5		
1982	654	977	17	17		
1983	1,853	2,830	50	50		
1984	4,508	7,338	132	138		
1985	7,824	15,162	340	335		
1986	8,003	23,166	696	679		
1987	4,779	27,945	1,137	1,155		
1988	2,002	29,947		1,704	1,603- 1,806	3,984- 4,187
1989	712	30,658		2,251	2,117- 2,385	6,168- 6,505
1990	238	30,896		2,719	2,557- 2,881	8,822- 9,289
1991	78	30,974		3,045	2,863- 3,226	11,804- 12,395
1992	25	30,999		3,187	2,997- 3,377	14,936- 15,638
1993	8	31,008		3,134	2,948- 3,321	18,023- 18,819
1994	3	31,010		2,905	2,732- 3,078	20,893- 21,760
1995	1	31,011		2,542	2,390- 2,693	23,409- 24,328
1996	0	31,011		2,101	1,976- 2,226	25,493- 26,446
1997	0	31,012		1,642	1,544- 1,740	27,125- 28,097
1998	0	31,012		1,213	1,140- 1,285	28,332- 29,315
1999	0	31,012		847	796- 897	29,176- 30,165
2000	0	31,012		559	525- 592	29,734- 30,724
2001	0	31,012		348	327- 369	30,082- 31,073
2002	0	31,012		205	193- 217	30,287- 31,278
2003	0	31,012		114	107- 121	30,401- 31,392
2004	0	31,012		60	57- 64	30,461- 31,453
2005	0	31,012		30	28- 32	30,491- 31,483
2006	0	31,012		14	13- 15	30,505- 31,497

TABLE 2B

Reconstructed and projected logistic HIV epidemic curve (with predicted AIDS epidemic) that yields the best fitting AIDS epidemic curve for homosexual/bisexual men in the Fed. Rep. Germany (1982-1987); m=8 years.

Source of AIDS incidence data: WHO Collaborating Centre on AIDS (Paris). Data are corrected for reporting delays by authors.

	HIV		AIDS			
Year	Annual Expec.	Cumul. Expec.	Annual Obs.	Annual Expec.	Annual 95% Conf. Int.	Cumul. 95% Conf. Int.
1976	1	1		0		
1977	1	2		0		
1978	5	7		0		
1979	15	22		0		
1980	48	70		1		
1981	152	221		4		
1982	465	686	11	11		
1983	1,307	1,993	39	35		
1984	2,924	4,916	86	95		
1985	4,158	9,074	230	218		
1986	3,256	12,331	402	413		
1987	1,556	13,887	686	661		
1988	570	14,457		929	758- 1,100	2,196- 2,538
1989	188	14,644		1,179	962- 1,395	3,270- 3,822
1990	60	14,704		1,376	1,123- 1,629	4,548- 5,296
1991	19	14,723		1,495	1,220- 1,769	5,953- 6,881
1992	6	14,729		1,521	1,242- 1,800	7,396- 8,480
1993	2	14,730		1,456	1,188- 1,723	8,789- 9,998
1994	1	14,731		1,314	1,072- 1,555	10,057- 11,358
1995	0	14,731		1,119	913- 1,325	11,144- 12,508
1996	0	14,731		900	735- 1,066	12,025- 13,429
1997	0	14,731		685	559- 810	12,698- 14,124
1998	0	14,731		492	401- 582	13,184- 14,622
1999	0	14,731		334	272- 395	13,515- 14,958
2000	0	14,731		214	174- 253	13,728- 15,173
2001	0	14,731		129	106- 153	13,857- 15,303
2002	0	14,731		74	60- 87	13,931- 15,377
2003	0	14,731		40	33- 47	13,970- 15,417
2004	0	14,731		20	17- 24	13,991- 15,437
2005	0	14,731		10	8- 12	14,000- 15,447
2006	0	14,731		4	4- 5	14,005- 15,451

TABLE 2C

Reconstructed and projected logistic HIV epidemic curve (with predicted AIDS epidemic) that yields the best fitting AIDS epidemic curve for homosexual/bisexual men in the U.K. (1982-1987); m=8 years.

Source of AIDS incidence data: WHO Collaborating Centre on AIDS (Paris). Data are corrected for reporting delays by authors.

Year	HIV		AIDS			
	Annual Expec.	Cumul. Expec.	Annual Obs.	Annual Expec.	Annual 95% Conf. Int.	Cumul. 95% Conf. Int.
1976	0	0		0		
1977	0	0		0		
1978	1	1		0		
1979	5	6		0		
1980	21	27		0		
1981	90	117		2		
1982	372	489	7	7		
1983	1,322	1,811	24	26		
1984	2,953	4,764	93	83		
1985	2,849	7,613	187	192		
1986	1,211	8,824	366	347		
1987	334	9,158	505	524		
1988	80	9,239		698	574- 822	1,754- 2,003
1989	19	9,257		845	694- 995	2,528- 2,918
1990	4	9,261		944	776- 1,112	3,410- 3,925
1991	1	9,262		984	808- 1,159	4,339- 4,963
1992	0	9,263		960	789- 1,131	5,256- 5,967
1993	0	9,263		881	724- 1,038	6,104- 6,881
1994	0	9,263		761	626- 897	6,842- 7,665
1995	0	9,263		619	509- 730	7,447- 8,299
1996	0	9,263		475	390- 559	7,913- 8,782
1997	0	9,263		343	282- 404	8,252- 9,129
1998	0	9,263		233	191- 274	8,482- 9,364
1999	0	9,263		149	122- 175	8,631- 9,513
2000	0	9,263		89	74- 105	8,720- 9,603
2001	0	9,263		51	42- 60	8,770- 9,654
2002	0	9,263		27	22- 32	8,797- 9,680
2003	0	9,263		13	11- 16	8,810- 9,694
2004	0	9,263		6	5- 7	8,816- 9,700
2005	0	9,263		3	2- 3	8,819- 9,703
2006	0	9,263		1	1- 1	8,820- 9,704

TABLE 2D

Reconstructed and projected logistic HIV epidemic curve (with predicted AIDS epidemic) that yields the best fitting AIDS epidemic curve for IVDUs in Italy (1984-1987); m=8 years.

	HIV		AIDS			
Year	Annual Expec.	Cumul. Expec.	Annual Obs.	Annual Expec.	Annual 95% Conf. Int.	Cumul. 95% Conf. Int.
1978	0	0		0		
1979	0	0		0		
1980	0	0		0		
1981	2	2		0		
1982	14	15		0		
1983	119	134		1		
1984	993	1,127	12	12		
1985	5,994	7,121	87	82		
1986	10,897	18,018	270	295		
1987	3,796	21,815	687	650		
1988	536	22,350		1,090	884- 1,296	1,925- 2,337
1989	63	22,413		1,547	1,254- 1,840	3,320- 4,036
1990	7	22,420		1,957	1,587- 2,328	5,120- 6,150
1991	1	22,421		2,264	1,836- 2,692	7,229- 8,569
1992	0	22,421		2,425	1,967- 2,884	9,513- 11,136
1993	0	22,421		2,424	1,966- 2,883	11,816- 13,681
1994	0	22,421		2,270	1,840- 2,699	13,992- 16,045
1995	0	22,421		1,994	1,617- 2,372	15,919- 18,106
1996	0	22,421		1,646	1,335- 1,958	17,522- 19,796
1997	0	22,421		1,276	1,035- 1,518	18,773- 21,098
1998	0	22,421		929	754- 1,105	19,689- 22,040
1999	0	22,421		635	515- 755	20,318- 22,681
2000	0	22,421		407	330- 484	20,722- 23,090
2001	0	22,421		244	198- 290	20,965- 23,335
2002	0	22,421		137	111- 163	21,102- 23,472
2003	0	22,421		72	58- 85	21,173- 23,544
2004	0	22,421		35	28- 42	21,208- 23,579
2005	0	22,421		16	13- 19	21,224- 23,595
2006	0	22,421		7	5- 8	21,231- 23,602
2007	0	22,421		3	2- 3	21,234- 23,605
2008	0	22,421		1	1- 1	21,235- 23,606

TABLE 2E

Reconstructed and projected logistic HIV epidemic curve (with predicted AIDS epidemic) that yields the best fitting AIDS epidemic curve for IVDUs in Spain (1984-1987); m=8 years.

Year	HIV Annual Expec.	HIV Cumul. Expec.	AIDS Annual Obs.	AIDS Annual Expec.	AIDS Annual 95% Conf. Int.	AIDS Cumul. 95% Conf. Int.
1978	0	0		0		
1979	0	0		0		
1980	1	1		0		
1981	5	6		0		
1982	31	38		0		
1983	185	223		3		
1984	1,024	1,247	15	15		
1985	4,129	5,376	74	71		
1986	6,695	12,070	213	221		
1987	3,182	15,253	473	467		
1988	705	15,957		774	708- 840	1,486- 1,618
1989	125	16,082		1,095	1,002- 1,188	2,533- 2,761
1990	21	16,103		1,385	1,267- 1,503	3,868- 4,196
1991	4	16,107		1,603	1,467- 1,740	5,422- 5,849
1992	1	16,107		1,721	1,575- 1,868	7,098- 7,616
1993	0	16,107		1,725	1,578- 1,872	8,784- 9,380
1994	0	16,107		1,622	1,483- 1,760	10,375- 11,032
1995	0	16,107		1,432	1,310- 1,554	11,785- 12,486
1996	0	16,107		1,189	1,088- 1,290	12,960- 13,689
1997	0	16,107		928	849- 1,007	13,880- 14,626
1998	0	16,107		682	624- 740	14,557- 15,312
1999	0	16,107		470	430- 510	15,025- 15,785
2000	0	16,107		305	279- 331	15,329- 16,090
2001	0	16,107		185	169- 201	15,514- 16,276
2002	0	16,107		106	97- 114	15,619- 16,382
2003	0	16,107		56	51- 61	15,675- 16,438
2004	0	16,107		28	26- 30	15,704- 16,466
2005	0	16,107		13	12- 14	15,717- 16,479
2006	0	16,107		6	5- 6	15,722- 16,485
2007	0	16,107		2	2- 3	15,725- 16,487
2008	0	16,107		1	1- 1	15,726- 16,488

Goodness of fit

In all cases the value of the coefficient of determination R^2 is larger than 0.99 which shows that the model fits the data well (Table 1). The good fit can also be assessed for m=8 years by comparing in Tables 2A - 2E the observed and expected values of the annual incidence of AIDS.

The good fit implies that the estimated variances of the model's error terms are small, which in turn leads to relatively narrow confidence intervals. In 2000 the upper limit of the 95% confidence interval for the cumulative number of AIDS cases is between 3 and 11 percent above the lower limit (Table 1).

These confidence intervals are smaller than the ranges observed between a median incubation period of 8 years and a median incubation period of 12 years. This shows that the projections are more sensitive to model-specification errors than to the statistical errors obtained for a given model that is assumed correct. The fact that the fit is equally good for a median incubation period of 8 years as for a median of 12 years shows that the results cannot be used to discriminate between the assumed density functions of the incubation period and that a median of 8 years is just as likely as a median of 12 years. This observation corroborates similar ones made elsewhere (Taylor, 1989).

Finally, the model was also fitted by minimizing Pearson's $\chi^2 = \Sigma$ (Expected cases - observed cases)$]^2/$ expected cases] (the expected values in the denominator are no longer squared, as with the SFS). This was done in order to investigate the sensitivity of the results to the criterion used to estimate the parameters. In each of the three western countries (France, Federal Republic of Germany, United Kingdom) the total number infected by the end of the century is 27,000, 16,000 and 9,000 instead of 31,000, 15,000, and 9,000, respectively (when m=8 years). In the southern countries, the corresponding totals were 29,000 instead of 22,000 for Italy, and 18,000 instead of 16,000 for Spain. The difference is small between the two criteria for the western countries, and somewhat larger for the southern countries (probably because there are fewer cases and data points, which explains the greater sensitivity to the criterion chosen).

Initial doubling time of HIV infections

The estimated value of the parameter r of the logistic equation (1) is of interest since it represents the growth rate of the cumulative number H(t) of infected individuals during the initially exponential phase of the epidemic; r is inversely related to a numerically more meaningful parameter, namely the doubling time (t_d) of the cumulative number H(t). Expressed in months, t_d is equal to $12\ln(2)/r$. As can be seen from Table 1 the estimated doubling time is 4 months in Italy, 5 months in Spain, 6 months in the United

Kingdom and Spain, and 7 months in France and the Federal Republic of Germany. (For each country the value of t_d, when it is rounded to the nearest month, is the same regardless of the incubation period.) These doubling times are plausible in view of our current state of knowledge (May and Anderson, 1987), and are much less sensitive to the median incubation period than is the total size of the epidemic.

Sensitivity to first year of HIV epidemic

For the western countries the results are not sensitive to the first year Y1 of the HIV epidemic. For example, if Y1 is taken as 1978 (instead of 1976) then for a median incubation period m of 8 years the total number of homosexual/bisexual men infected by the end of the century in France, the Federal Republic of Germany, and the United Kingdom is 30,932, 14,694, and 9,597 instead of 31,012, 14,731 and 9,262, respectively. If Y1 is 1974 (instead of 1976) the corresponding totals by 2000 are 32,277, 13,981, and 9,295. In all cases the coefficient of determination R^2 is larger than 0.99. This shows that for these countries the results are not very sensitive to the first year of the HIV epidemic.

In the southern countries, however, the results are more sensitive to the first year of the HIV epidemic. In Italy, the total numbers infected are 37,528 (Y1=1980) and 22,919 (Y1=1976) instead of 22,421 if Y1=1978 (with m=8 years). In Spain the corresponding totals are 24,845 (Y1=1980) and 15,752 (Y1=1976) instead of 16,107 if Y1=1978. For both countries the difference is small when Y1 shifts from 1978 to 1976, but much larger when Y1 shifts from 1978 to 1980. In all cases R^2 is above 0.99. As for the sensitivity to the criterion chosen, the results are more sensitive for the southern countries than for the western countries, and probably for the same reasons: results are more sensitive when there are fewer cases and data points.

DISCUSSION

Model assumptions

The assumption of a logistically growing HIV infection leads to a model-based reconstruction of the HIV epidemic curve, which after extrapolation provides plausible projections of the AIDS epidemic within a homogeneous risk group. This crucial homogeneity assumption precludes the possibility of an epidemic that would for example begin in large cities, then slow down because of saturation, and only later seep into the rest of the country with renewed vigor. Such a scenario of geographic heterogeneity cannot be accounted for by a logistic modeling of the HIV epidemic.

The model, which fits the data well regardless of the assumed median incubation period, shows that in order to account for the decline in the growth rate of AIDS, the spread of HIV must have peaked around 1985 for homosexual/bisexual men in the three western countries, and around 1986 for IVDUs in the two southern countries. This result is in keeping with the notion of an epidemic that spread quickly and saturated the susceptible population over a short period of time.

Extreme caution should be exercised, however, when interpreting results based on a model with three parameters (A, B, and r) that is fitted to four or six data points. In the cases of Italy and Spain for example, it is not surprising that we can fit the three-parameter model well to four data points. The model should be tested in the future with more data in order to better assess its validity.

The fact that the model fits the data well does not necessarily imply that the model is correct. Besides, which model would be the correct one? The model with a median of 8 years, or the one with a median of 12 years? Good fits can be obtained for different incubation periods, but also for very different parametric forms for the reconstructed HIV epidemic curve or the density of infection times (Hyman and Stanley, 1988; Centers for Disease Control, 1987; De Gruttola and Lagakos, 1989). These different parametric forms can yield very different HIV epidemics that produce modeled AIDS epidemics which fit the data equally well. It is therefore with caution that conclusions should be drawn from one particular functional form for the HIV epidemic – and a good case needs to be made for the use of one form rather than another.

The logistic growth curve was chosen as a model for the spread of HIV because:

1. It provides a simplified model of the transmission dynamics of HIV under the assumption of homogeneous mixing.
2. It allows for an upper limit in the number of infected persons.
3. Its parameters are epidemiologically meaningful.

For these reasons the logistic is a good candidate as a long-run model of the growth of HIV infection. The plausibility of the results are now discussed separately for both risk groups.

Homosexual/bisexual men

There are some ancillary data that support our model's conclusions. For example, recent work suggests HIV may already be spreading more slowly in the Federal Republic of Germany (Maxeiner and Habermehl, 1989). Also, in 1988 the World Health Organization has released estimates of the known number of infectives in each European country (see Artzrouni and Heilig, 1988). Although these estimates represent minimum levels of HIV prevalence, they are in good agreement with the reconstructed HIV epidemics obtained here. For example, the Federal Republic of Germany reported 33,906 known infectives, for all risk groups combined, (AIDS-Zentrum am BGA, 1989). If roughly sixty-five percent of those are homosexual/bisexual men, this means there were about 22,000 known infected homosexual/bisexual men. From Table 2B we see that the cumulative number of infected German homosexual/bisexual men by 1988 was reconstructed as being about 14,500 if m=8 years. If m=12 years the number is 36,000. This is a wide, but certainly plausible interval.

Similarly, the United Kingdom reported 8,000 known infectives in all risk groups. Recent calculations, however, put the number anywhere between 20,000 and 100,000 (Rees, 1989). These estimates do not disagree with our reconstructions which produce between 9,000 (m=8 years) and 24,000 (m=12 years) homosexual/bisexual men infected in the United Kingdom.

The slowdown in the spread of HIV implied by the model is so rapid that between 1990 and 1995 in France, the Federal Republic of Germany, and the United Kingdom there would be only 353, 88, and 5 newly infected homosexual/bisexual men, respectively (for m=8 years, Table 2A-2C; the numbers are slightly higher if m=12 years). The model projects no new infections after 1995.

Although not impossible, this dramatically rapid saturation of the epidemic among homosexual/bisexual men may not be fully realistic. It should be remembered that the logistically modeled HIV epidemic is a highly stylized representation of reality, that does not account for a residual epidemic that may continue at a low level after the major epidemic has passed. For example, as new cohorts of homosexuals become sexually active, not all of them will adopt low-risk sexual practices. Until a vaccine is found HIV could thus continue to spread, but at a level well below the threshold needed for the epidemic to flare up again (the same comments apply to the epidemic among IVDUs).

When looking at the epidemic from the AIDS perspective, there are signs that the projections developed here may at least qualitatively be on the mark. Indeed, The WHO Collaborating Center on AIDS reported in March 1989 that a leveling off of AIDS cases may already be occurring in several northern and western European countries, where the bulk of the epidemic is made up of homosexual/bisexual men (WHO Collaborating Center on AIDS, 1989). This suggests that our projected leveling off of the AIDS epidemic in the early to mid-1990s, at least for the western countries, is plausible and may have already started.

Intravenous drug users

The results suggest that the same rapid saturation has occurred among southern IVDUs as has occurred among homosexual/bisexual men in western countries. For both southern countries and both incubation periods the HIV epidemic is reconstructed as having peaked in 1986. After 1990 there are only 8 new infections in Italy and 26 new infections in Spain (for m=8 years). This result clearly implies a rapid saturation of the epidemic that reflects the implicit assumption that the virus will not spread much beyond the groups of IVDUs already infected in large metropolitan areas of Spain and Italy. This assumption may not be unreasonable given that the extensive needle sharing among drug users is to a certain extent an urban phenomenon. It is in large cities that drug users congregate in shooting galleries and other meeting places where the repeated sharing of dirty syringes promotes the efficient spread of HIV. In small cities or rural areas there may be fewer needle sharing activities, and also more visibility and therefore greater risks for a person who abuses illegal drugs intravenously. It is therefore possible that the virus will not spread much among IVDUs in non-metropolitan areas. (Interestingly, the Swiss authorities are well aware of the importance of containing the activities of IVDUs to limited areas of cities. A park in Zürich is reserved for drug addicts, who are monitored around the clock by health authorities who provide them with clean needles and medical assistance when needed.)

As of January 1, 1988, there were fewer AIDS cases among Spanish and Italian IVDUs than among German and British homosexual/bisexual men (i.e., 775 and 1,056 IVDUs respectively in Spain and Italy, and 1,454 and 1,182 homosexual/bisexual cases in the Federal Republic and the United Kingdom). However, Tables 2A-2E show that the number of new AIDS cases in Italy is expected to overtake the numbers in the Federal Republic of Germany and the United Kingdom as early as 1988; the incidence in Spain is expected to overtake that in the two western countries by 1990.

The fact that the epidemic among southern IVDUs is expected to overtake the epidemic among German and British homosexual/bisexual men reflects the fact that the AIDS epidemic in the former group is younger and growing at a more sustained rate than in the latter group. This has resulted in a larger reconstructed HIV epidemic in the southern countries. Indeed, if m=8 years the model predicts that by the end of the century HIV will have claimed a total of about 22,000 IVDUs in Italy and 16,000 in Spain whereas only 15,000 and 9,000 homosexual/bisexual men are predicted to be infected in the Federal Republic of Germany and the United Kingdom. (Similar results hold if m=12 years; Table 1). Also, if m=8 years the maximum annual incidence of HIV infection is 11,000 and 7,000 in the southern countries but only 4,000 and 3,000 in the Federal Repub lic of Germany and the United Kingdom (even though the reconstruction is based on fewer AIDS cases in the southern countries; the results are similar if m=12 years).

Transients

Because HIV peaked so quickly after the onset of the epidemic, the initial exponential phase of the HIV epidemic was very short and therefore the positive transient in AIDS cases that occurs during the exponential phase of the epidemic may have occurred during a short period in the late 1970s, before AIDS was recognized. (A positive transient is the phenomenon by which the doubling time of the growth of AIDS declines during the initially exponential phase of the HIV epidemic (Gonzalez and Koch, 1987). Our results thus suggest that the currently observed increase in the doubling time of AIDS cases (= decrease in the growth rate), at least among homosexual/bisexual men and IVDUs, must be the result of a negative transient, i.e., is brought about by a decline in the growth rate of HIV. This obviously occurs here since the model suggests that in all cases the annual incidence of HIV infection has actually decreased in the mid 1980s. Although this qualitative conclusion is insensitive to the model's parameters, the ultimate size of the epidemic is quite sensitive to the median incubation period.

Data assumptions

The procedure assumes that the data is accurate – which we know it is not. Indeed, there is underreporting of AIDS, and the magnitude of this underreporting is unknown. However, if these errors result in an across-the-board underestimate of ten or twenty percent that *has not changed through time*, then the projections obtained here can simply be inflated by the corresponding correction factor. The results would not be *qualitatively* changed, i.e, the HIV epidemic would still have peaked around 1985 for homosexual/bisexual men in the three western countries and around 1986 for IVDUs in the two southern countries. If the magnitude of the underreporting errors has changed significantly through time, and if for example the true number of AIDS cases is still growing exponentially, then of course the results presented here are invalid.

Finally, the model and procedure assume that the fraction f of infected individuals who develop AIDS is 1. Although it is thought that f may be 1 there is still some uncertainty concerning its true value (Anderson and May, 1988; Lui *et al.*, 1988). In any event, the results obtained with f=1 can immediately be transposed to the case f<1: everything remains unchanged except that the reconstructed and projected epidemic curves of HIV infections obtained with f=1 must simply be inflated by a factor equal to 1/f. If, for example, it is believed that f=0.7, the epidemic curves of HIV infection must be multiplied by 1/0.7 = 1.43, since only 70 percent of these individuals will develop AIDS. The predicted numbers of AIDS cases then remain unchanged.

CONCLUSION

The wide range of forecasts obtained here for the future course of AIDS in five European countries reflect our ignorance concerning the transmission dynamics of HIV and concerning the behavioral determinants of the spread of the virus. These gaps in our knowledge are exacerbated by the lack of precise data concerning key epidemiological parameters of the epidemic (e.g., the incubation period). When making long-term projections, these problems are compounded by our inability to predict medical discoveries (vaccines and treatments) and to anticipate future behavioral changes (how will young people who become sexually active in the future react to the threat of AIDS? What will be the impact of changing societal responses to the epidemic? etc.). These unknowns must be added to the considerable uncertainties surrounding the model, its parameters, and the data, when attempting an overall assessment of long-term projections of AIDS.

Clearly, the uncertainties concerning the model, coupled with our inability to predict medical breakthroughs (or lack thereof) imply that the long-term projections developed here must be viewed as *conditional orders of magnitudes only*, and not as precise forecasts (conditional on a number of well defined assumptions, that can always be questioned).

For example, the logistic growth curve for the spread of HIV infection is an oversimplified stylization of the complex transmission dynamics of HIV in a homogeneous risk group. However, if we assume that HIV continues to spread fairly homogeneously among homosexual/bisexual men and IVDUs and does not penetrate new communities among these groups at recognized risk, then the *qualitative results* may be of some relevance, since an almost complete HIV epidemic was reconstructed on the basis of observed cases of AIDS to date. Indeed, the model suggests that in the five European countries considered here, the AIDS epidemic could soon saturate the two communities of homosexual/bisexual men and IVDUs who could reach their peak incidences in the early to mid 1990s – if for no other reason than because of the depletion of susceptibles within these groups. The model also suggests that the rapidly growing epidemic among IVDUs in the two southern countries will soon overtake the epidemic among German and British homosexual/bisexual men.

In short, the present work does not provide answers concerning the future course of the whole AIDS epidemic in Europe. It does, however, offer plausible scenarios for the future of AIDS among homosexual/bisexual men and IVDUs. The news is mixed: on the one hand we may be seeing the end of the tunnel with a leveling off of the AIDS epidemic in these groups in the early to mid 1990s; on the other hand, the long incubation period insures that the epidemic will be protracted and could affect by the year 2000 between 55,000 (m=8 years) and 139,000 (m=12 years) homosexual/bisexual men in France, the Federal Republic of Germany, and the United Kingdom. In Italy and Spain infection with HIV could claim by 2000 between 39,000 (m=8 years) and 106,000 (m=12 years) IVDUs. These are staggering numbers that leave no room for complacency in Europe's fight against the human immunodeficiency virus.

Technical note: The model was implemented in BASIC and run on a microcomputer. The first author has developed a user-friendly software that prompts the user for the number of AIDS cases that was diagnosed each year and the desired median incubation period. After a few minutes of calculations the program produces the results in the form of Tables 2A-2E. This software, which can be used to project the future course of the HIV and AIDS epidemics in a given risk group, is available from the first author for a nominal fee to cover postage and handling (for both IBM-PC compatible computers and MacIntoshes).

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