Journal of Acquired Immune Deficiency Syndromes
3:403–412 © 1990 Raven Press, Ltd., New York

Special Feature

The Global Epidemiology of HIV Infection: Continuity, Heterogeneity, and Change

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Three major epidemiological patterns of HIV infection have been previously described in the world. In pattern I, which occurs mainly in North America, Europe, and Australia, most cases occur in homosexual men and injecting drug users and their sex partners and offspring. Pattern II occurs mainly in sub-Saharan Africa, and increasingly in other parts of the world. Here, most people acquire their infection heterosexually, perinatally from their mother, or through blood transfusion. Finally, pattern III includes the remaining countries where HIV was very recently introduced and where small numbers of cases have been infected in various ways (1). However, this situation is far from being a static one, and in this review we will focus on the changing trends in the epidemiology of HIV infection, as well as on the impact of HIV infection on health and society, with emphasis on the developing world.

EPIDEMIOLOGIC TRENDS

What are the trends in the world? First of all, the number of new cases continues to increase but the future HIV trends are uncertain. In order to assemble the best estimates of experts, the World Health Organization undertook a Delphi survey. The survey results estimated that there would be as many as 6 million cases of AIDS and nearly 14 million cases of HIV infection in the world by the year 2000, as compared with estimated cumulative numbers of less than 1 million and 5.1 million, respectively, by the end of the 1980s (2). More than one-half of the approximately 5 million AIDS cases that are projected for the next decade are likely to occur regardless of how effective HIV/AIDS prevention efforts may be, since the AIDS cases will be developing in those persons infected with HIV prior to 1989. Finally, and sadly enough, AIDS prevention programs are projected to be potentially capable of preventing only one-half of the new HIV infections that will develop between 1988 and 2000.

Many of the countries where the virus has been introduced more recently are experiencing as rapid or more rapid rates of growth of AIDS cases as those where the epidemic started earlier. This is particularly obvious when comparing the situation in many Latin American countries with the U.S. (3). This rather discouraging situation is probably due to infections acquired in the early 1980s.

These observations should stimulate countries without a large AIDS problem as yet to give high priority to the primary prevention of HIV infection. It is crucial that such countries assess whether they have large populations at potential risk for the spread of HIV in order to target groups for preventive programs. Countries with large young urban populations, high rates of sexually transmitted diseases (STDs), and/or a problem of intravenous drug use are likely to be the most at risk, if they do not have an HIV problem already. In contrast, rural populations with very low rates of STDs, or drug use are likely to be less affected. Distinguishing between these scenarios will require strengthening ad-

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Presented at the Vth International Conference on AIDS, Montreal, June 1989.

equate epidemiological monitoring of STDs and intravenous drug use in all countries.

A recent tragic example of the sudden emergence of HIV infection in a vulnerable population is the fulminant spread of the virus among injecting drug users in Thailand, modifying completely that country's HIV/AIDS problem. Whereas in 1986 the HIV prevalence in this country's drug abusing population was virtually zero, by 1988 the prevalence rate had increased to over 40% (4). The previous epidemiologic status was preliminary and fragile, but the presence of dense urban populations with high rates of i.v. drug use, prostitution, and STDs provided a warning (4) (Fig. 1).

A second trend is the heterogeneous speed of spread of HIV in those populations where the virus has now been present for some time. This was first noted when HIV prevalence rates in the general population were compared with populations at high risk for HIV infection such as female prostitutes in Africa or homosexual men and i.v. drug users in some parts of North America and Europe (Fig. 1). Even in populations in Africa who are not at particularly high risk, HIV spreads more rapidly in some groups than in others. Figure 2 shows how over a period of 2 to 3 years the HIV seroprevalence rates more than doubled in pregnant women in Uganda and selected samples in the general population in the Central African Republic, whereas in Kinshasa, Zaire, the rate remained fairly stable over a 5 year period (5–7). Even though these figures should be interpreted with much caution, since we cannot determine the role that selection bias may have played, the differences are so striking that they are probably reflecting some real situation.

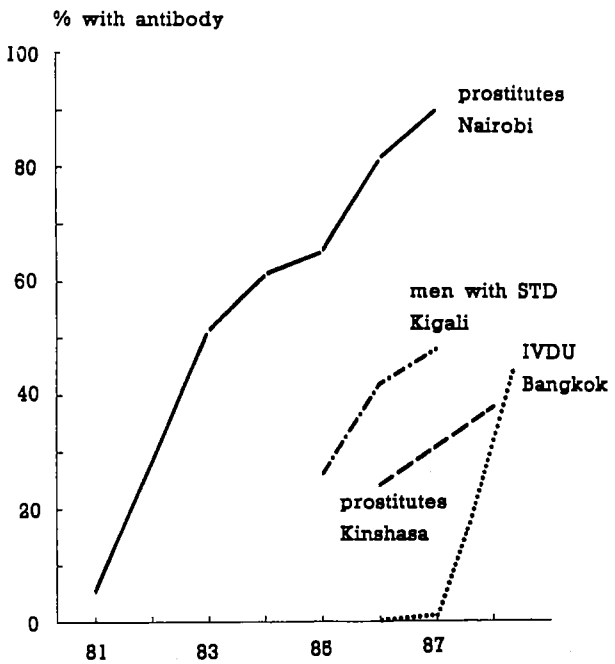

FIG. 1. HIV-1 antibody prevalence rates over time in high-risk populations.

There is also a major difference in Africa between the cities and the rural areas, where two-thirds of the African population still lives. A carefully done nationwide health survey in Rwanda reveals a sobering picture: over 20% of urban adults were infected with HIV in 1987 (8). This study also shows that although a much lower infection rate was noted in rural adults, the 2% rate observed in this population group was certainly not negligible. Also, the trend toward urbanization brings problems that complicate the control programs for HIV infection and STDs as now exist in the urban U.S.A. (9,10).

A third indicator of the dynamism of this epidemic is the shift in transmission groups among AIDS cases. This is very obvious in Latin America, which WHO now classifies as a "Pattern II/III" area (11). Thus, whereas in the early years (1982–1985) of the epidemic in Brazil the overwhelming majority of AIDS cases were highly educated homosexual men, this was not the case any longer in 1988 (12). Currently, more women, more less educated people, and more injecting drug users are among the AIDS victims in Brazil. This is a trend also being observed in North America and Europe. It is estimated that by 1990 there will be more new cases of AIDS among the intravenous drug using population than among the homosexual male population of the European Community (13).

Finally, an epidemiological pattern may also be determined by the type of virus. Despite its first recognition several years ago in West Africa, little is known about the epidemiology and clinical expression of HIV-2 infection. It is remarkable that HIV-2 seems to spread at a much more limited rate in Africa than HIV-1, which is rapidly becoming the predominant human immunodeficiency virus in most West African countries (16). In addition, whereas HIV-2 infection rates as high as 8.9% were found in adults in a community-based survey in Guinea-Bissau, HIV-2 antibody was virtually absent among infants and young children (14). This suggests that HIV-2 is transmitted less efficiently from mother to child than HIV-1, though such transmission certainly occurs, as illustrated by cases in Côte d'Ivoire (15). More carefully con-

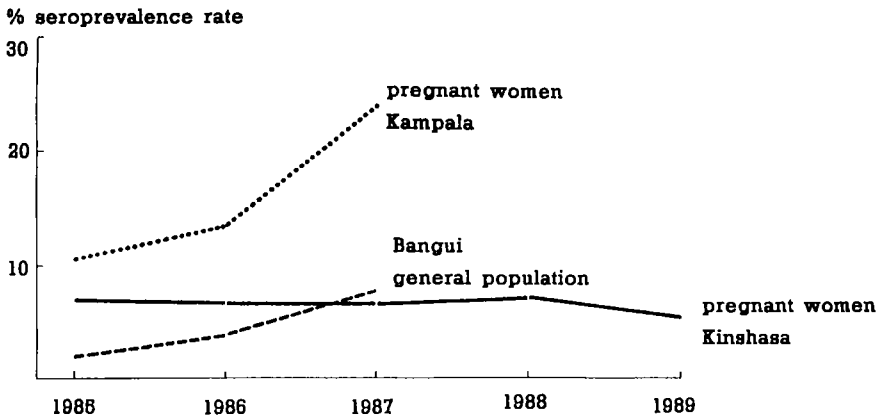

FIG. 2. HIV-1 antibody prevalence rates over time in three African populations.

ducted studies are needed to understand the differences, if any, in infectivity and pathogenic potential of HIV-2 as compared to HIV-1.

REASONS FOR DIFFERENT EPIDEMIOLOGIC PATTERNS

Why are all these patterns occurring? Several factors are probably simultaneously at work. They include demographic, behavioral, and biological variables, and perhaps political and economic reasons as well (Table 1). It is their subtle interaction that determines how and where HIV spreads in populations.

Demography

The demographic structure of the population in the developing world plays a very important role in determining the observed higher incidence of sexually transmitted diseases in these regions as compared to the industrialized world; the sexually most active age groups represent a much larger proportion of the population in the developing world than in Europe or North America. Also, as a result of continuing high birth rates, this potentially "at-risk" population of adolescents and young adults in the developing world will become even larger in the next decades.

Recent data from West Africa show that the sex ratio of AIDS cases in Africa is not always approaching one. Whereas in Central Africa there appear to be slightly more female cases, men outnumber female patients by a factor of 2 to 4 in Côte d'Ivoire and Senegal (16–19) (Table 2). These observations should clearly be confirmed by community-based surveys, but are nevertheless intriguing and again illustrate the diversity of the epidemiologic patterns of HIV infection in sub-Saharan Africa. It is striking that the sex ratios in different African cities are also very variable. In general, cities in East and Southern Africa have a large excess of men, mainly due to migration of male labor into cities created during colonial times. For instance, it is estimated that there are 50% more men than women in a city like Nairobi (20). In other parts of

TABLE 1. *Variables affecting the spread of HIV infection in populations*

Demographic variables
High proportion of sexually most active age groups
Male to female ratio in the population
Rapid urbanization
Existence of major roads
Behavioral variables
Rate of partner change
Type of sexual intercourse (receptive anal intercourse, intercourse during menses)
Size of and rate of contact with core groups
Behavior of partners (IVDU, bisexuality, etc.)
Biological variables
Presence of other sexually transmitted diseases
Clinical stage of HIV infection (CD4-cell depletion)
Infectivity of viral strains
Male circumcision (?)
Political/economic variables
Response to the epidemic
Performance of health care system
War, civil disturbance

TABLE 2. *Sex ratio of AIDS cases and 20–39 year olds in Africa*

		Male to female ratio	
Location	Year	AIDS cases	Urban 20–39 years
Abidjan	1988	4.6:1	1.2
Dakar	1988	2.4:1	0.9
Kinshasa	1987–1988	0.8:1	0.9
Uganda	1987–1988	0.9:1	1.0

Based on refs. 16–20.

the continent, there seems to be a more equal distribution of the sexes. It is likely that such urban demographic patterns have a marked influence on sexual behavior patterns by disrupting the family unit and by encouraging prostitution and high rates of STDs. In fact, prior to the emergence of AIDS, recent STD trends in Nairobi (1970s) were similar to those seen during wartime in Southeast Asia, when tens of thousands of men migrated to urban centers. In other parts of the continent, there seems to be a more equal distribution of the sexes.

Behavior

The rate of sexual partner change, the type of sexual intercourse and the nature of partners with whom one mixes are all critical in determining the spread of a sexually transmitted infection (21). In general, sexual behavioral patterns that involve contacts with a small but highly infected core group are associated with the most rapid spread of HIV, just as for gonorrhea (9). This may be the case in several African urban populations currently experiencing an HIV epidemic. However, overemphasis on prostitution as an explanation for the spread of HIV is an inadequate portrayal of urban sexual behavior in much areas of Africa (20). In many countries, the predominant sexual pattern may involve roughly equal numbers of men and women who have a small but dynamic, fluid set of simultaneous or serial lovers. At least during the initial phase of an epidemic when the prevalence in the general populations is still low, this latter pattern probably implies a slower spread of HIV due to relatively limited exposure of infected persons to others.

This complex interaction of behavior is illustrated by community-based data on employed couples with HIV infection in Kinshasa, Zaire (22). As in clinic-based studies elsewhere in the world, in only approximately 15% of the couples with at least one infected spouse were both partners infected. As in reports from several other countries, there were as many discordant couples with an infected wife as with an infected husband, showing that in this population at least both sexes are engaged in pre- or extramarital sex. In addition, a history of sex with a prostitute was a risk factor for being HIV positive in the husbands.

Biology

Prospective studies in female prostitutes in Kenya and Zaire found a much higher incidence of various STDs, including genital chlamydial infection, genital ulcers, and even trichomoniasis, among women who seroconverted for HIV antibody, as compared to women who remained seronegative. This remained so after controlling for self-reported sexual exposure and condom use (23–26).

With all of these significant relative risks emerging, more attention should be given to the population-attributable risk of various variables, in other words the proportion of cases of HIV infection that have occurred because these risk factors were present and perhaps would not have occurred in their absence. Estimates for the latter require the very restricted assumption that certain individuals would not acquire HIV in the absence of the risk factor—in fact, the acquisition may only be delayed. On one hand, it is striking that of 36 seroconverting women in Kinshasa, only 1 did not experience an STD before seroconversion (26), suggesting that the risk of acquiring HIV in the absence of STDs is much lower indeed, or that the behaviors causing HIV infection are uncommon in people who do not also acquire others STDs. On the other hand, if it is confirmed that common STDs such as trichomoniasis are increasing the risk of HIV infection, then they will represent a much higher population-attributable risk than genital ulcers, which are less common. However, it may be that population-attributable risks cannot be realistically calculated in populations with so many confounding factors.

If these data reinforce the need for effective STD control programs (focusing on all major STDs, not just genital ulcer disease) in conjunction with HIV prevention programs, it remains important to know how to intervene. For instance, would the distribution of condoms, which prevent STDs *and* HIV, have a greater effect than a strategy aiming at treatment of genital ulcer disease?

There may be other phenomena that influence HIV transmission at the local genital level. Receptive anal intercourse is a well-documented risk factor for homosexual men, although less so for heterosexuals (27,28). Sex during menses appears to increase the risk of female-to-male transmission, as found in a multicenter European study (27).

Being uncircumcised for men is less well established as a risk factor for HIV transmission. It was identified as such in Nairobi, and subsequently a correlation was found between being uncircumcised and high HIV seroprevalence rates in parts of Africa (24,29–31). However, Patter analysis by country failed to control for the time of introduction

of HIV in a population, and for other potential or established factors that influence the spread of HIV. Other studies in Africa or the U.S. failed to confirm this association (26,32,33). Similarly, earlier findings on oral contraception as a risk factor for HIV infection (25) have not been confirmed (26,34,35). At the present time, it is premature to draw any practical conclusions from these preliminary studies on oral contraception and circumcision.

More and more studies provide examples of the extreme heterogeneity in sexual transmission of HIV. The average rate of transmission of HIV from a single sexual contact is usually low. Some people become infected after only one contact with an infected partner and some do not become infected after literally hundreds of sexual encounters with an infected person. It is now clear that this is not just a matter of chance, but is, in part, related to the infectivity of an individual at a particular time (36,37). Several studies have now shown that people with a more advanced clinical stage of disease or a more profound immunodeficiency are more infectious for their sex partner (26,38,39). However, one should bear in mind that healthy carriers will remain the largest source of HIV infection. That some individuals are high transmitters for other reasons is suggested by the occurrence of clusters of infected sex partners of a single individual with HIV infection (40). It may be that some viral strains are more infective in vivo, just as some viral isolates appear to replicate more efficiently in vitro (41–43).

From the discussion above, it appears that a hierarchy of risks will become apparent in the coming years that will predict problem areas for the spread of HIV. Whatever additional risk factors may play a role, it is essential to realize that sexual transmission does occur in the absence of such facilitating factors. Factors facilitating transmission of HIV are still incompletely understood, and not an all-or-nothing phenomenon. Explanations focusing on a single risk factor are too simplistic.

IMPACT OF HIV ON OTHER ENDEMIC DISEASES

HIV infection not only directly causes morbidity and mortality on its own or through well-recognized opportunistic infections, but it may also modify the clinical expression, natural history, and response to therapy of other endemic diseases as well. Such diseases are listed in Table 3.

Tuberculosis (TB) is perhaps the most important example of such an interaction. In New York City the risk of developing active tuberculosis is substantially elevated in individuals with HIV infection who are tuberculin positive compared to those who were not infected with HIV (44). Consequently, as a result of the spread of HIV, the incidence of tuberculosis is rising in several parts of the world. This represents an enormous challenge to TB control programs. Is antituberculous chemotherapy as effective in HIV-positive as in HIV-negative patients with tuberculosis? Data from an ongoing study in Kinshasa suggest two things: first, there are no more treatment failures among HIV-infected patients with tuberculosis, but second, the relative risk of a relapse of pulmonary tuberculosis after the end of therapy of newly diagnosed cases was 3.9% among HIV-positive patients, reaching 17% after one year, as compared to 4% in tuberculosis patients without HIV infection (45). Whether this represents relapse or reinfection is as yet unknown. However, it is important to point out that in this population high levels of primary resistance to antituberculous drugs may exist, and that a suboptimal antimicrobial regimen was used (streptomycin–isoniazid–thiacetazone) in the study. More optimal chemotherapy may yield better results in HIV-positivepatients.

The evidence for an impact of HIV infection on other diseases is less well documented (46,47). Case reports suggest that the clinical spectrum of syphilis and the rapidity of disease progression, particularly to neurological disease, may be modified by concomitant HIV infection (48–51). In addition, treatment failure may be more common in such patients. However, difficult, large prospective studies requiring invasive procedures such as repeat lumbar

TABLE 3. *Impact of HIV infection on other endemic diseases*

Disease (ref.)	Natural history	Response to therapy
Tuberculosis (44,45)	+	+
Syphilis (48–51)	+	+
Chancroid (55,56)	+?	+
Hepatitis B (52,53)	+	
Herpes simplex virus infection	+	
Genital human papillomavirus infection (54)	+?	
Measles (57,58)	+	
Leishmaniasis (46)	+	

punctures are necessary to adequately address these issues, particularly since syphilis itself in the absence of HIV infection has been poorly studied in recent times.

The clinical course of other STDs as well may be influenced by concomitant HIV infection. Reactivation of herpes simplex virus infection is common in patients with advanced HIV infection. People with prior HIV infection have a higher risk of becoming carriers of hepatitis B virus, and the response to hepatitis B vaccine is often inadequate (52,53). There is also evidence that HIV infection exacerbates cervical cytological abnormalities mediated by human papillomavirus, although the data are still preliminary (54). Chancroid, the most common cause of genital ulcer disease in the developing world, seems to respond less well to single-dose therapy in HIV-infected patients (55,56), although confirmation of these reports is needed.

Since sexually transmitted diseases and HIV infection tend to occur predominantly in the same populations, their interactions have implications for STD control programs and management of patients with STDs.

Several studies have documented a higher case fatality rate of measles in unvaccinated HIV-positive children, and a study in Nairobi suggests that the attack rate of measles is significantly higher before the age of 9 months in children born to HIV-seropositive mothers. Fortunately, the response to measles vaccine itself does not appear to be modified in the presence of HIV infection (57–59).

It seems probable that more diseases will be identified that are profoundly affected by HIV infection.

IMPACT OF HIV ON MOTHER AND CHILD HEALTH

A substantial proportion of women of childbearing age are now infected with the virus in many countries. So far, studies on the interaction of HIV infection and pregnancy have concentrated mainly on the issue of perinatal transmission of HIV. Whether HIV infection itself adversely affects pregnancy outcome remains uncertain. Whereas a recent prospective study did not find evidence for adverse pregnancy outcome among intravenous drug users in New York City (60), in a prospective study in Zaire and in a case control study in Kenya, maternal HIV infection was significantly associated with premature delivery, low birthweight, and stillbirth (35,61).

It is as yet not clear what the biological basis is for these complications, whether HIV is a marker or a cause, and how to explain these differences in pregnancy outcome between the various studies. Differences in the stage of HIV infection in the mother, and in diagnostic criteria, as well as the simultaneous occurrence of other risk factors for adverse pregnancy outcome such as i.v. drug use, are perhaps implicated.

Although there is now good evidence that HIV is transmissible through breast-feeding, the risk of transmission is not clear. Data from Projet SIDA suggest that the risk is low in Kinshasa relative to perinatal transmission (62), but a study in Zambia found that infants who were breast fed by HIV-positive mothers more often acquired HIV infection than infants who had received bottle feeding exclusively (63). Studies involving large sample sizes will be necessary to resolve this issue. However, for ethical reasons, controlled prospective trials on the effect of breast feeding on HIV transmission cannot be justified in developing countries. Implications of these data for public health policy may vary from country to country. In populations with a high incidence of infant and child mortality under 5 years of age as a result of various infections, promotion of breast-feeding is one of the most effective preventive strategies against child mortality. Even in areas with high rates of HIV infection this policy should not be changed.

There are also emerging data that HIV-positive women may be less willing or able to breast feed their children than HIV-negative women. In a prospective study in Kinshasa, seropositive women were much more likely to never breast feed or to wean at an earlier age their child than age- and parity-matched seronegative women. Given the known anti-infective properties of breast milk and its demonstrated protective effects against some infectious diseases, especially diarrhea, early weaning or even never beginning to breast feed a child born to a seropositive mother is likely to have an adverse effect on these children regardless of whether they acquired HIV infection from their mother.

The only alternative to promoting universal breast-feeding in developing countries is antenatal or intrapartum HIV screening to identify seropositive women before they begin to breast feed and strongly counsel these women not to breast feed their infants. However, the logistical and fiscal re-

straints of this strategy and the associated likelihood of an extremely low cost/benefit ratio associated with its implementation in less developed countries makes this alternative not very viable.

One thing is clearly measurable: the morbidity and mortality associated with perinatal HIV infection is very high in Africa.

While the adverse role that HIV infection plays on pregnant women has not yet been well defined, the detrimental impact that HIV infection plays on children born to HIV-positive women has become increasingly clarified. In a prospective study carried out in children born in Kinshasa, Zaire, during the first year of life there were 100 (21%) deaths among the 468 children of HIV-1-seropositive mothers compared with 23 (3.8%) deaths among the 604 concurrently followed children of seronegative mothers ($p < 0.001$) (61). Of the 341 infants of seropositive women who survived to 1 year, 27 (7.9%) had developed AIDS. Between 1 and 2 years of age, another 20% of the perinatally infected children died, whereas the curve for the noninfected children born to HIV-positive mothers parallels that of the control group (64). Similar observations were made in prospective studies in Nairobi and Brazzaville (65,66).

Perinatally acquired HIV infection was not the only cause of the increased death rate in infants born to HIV-positive mothers. It appears likely that many of the infants who died during the first year of life did not die directly from perinatally acquired HIV infection but as a result of HIV-induced complications in their seropositive mothers. Diarrhea and pneumonia were among the leading cases of death in infants born to seropositive women. Having a mother with HIV infection/AIDS appeared to place a child at increased risk of suffering adverse consequences from these other highly endemic childhood infections. A mother with AIDS may be less capable of providing the requisite mothering skills necessary for minimizing the morbidity and mortality that can so easily accompany the highly prevalent childhood diseases. A child of a mother with AIDS may be less likely to receive adequate treatment with oral rehydration solution for his/her diarrhea because the mother may not be able to pursue the appropriate health-seeking behavior for her child.

What is the impact of vertical transmission of HIV on child survival in Africa? This obviously depends in the first place on the prevalence of HIV infection in pregnant women. Valleroy et al. (67) calculated that whereas in cities like Maputo and Nairobi HIV contributes as yet little to infant mortality, in Kampala an average of 20% of infant deaths are due to HIV. This proportion will undoubtly increase in many countries. It is clear that mother and child health programs should become much more involved in AIDS prevention than is the case now, and that strategies to deal with HIV infection in children should be developed.

In adults as well, AIDS has become a major cause of morbidity and mortality. For instance, in Kinshasa, 50% of all medical patients were HIV positive in 1988, and in Abidjan, Côte d'Ivoire, between 15 and 20% of all male patients in medical wards in 1988 had AIDS (68,69). This is remarkable for a country where AIDS was only recognized as late as in 1985. Again, it illustrates how fast HIV can move, and that the disease is now well established in West Africa as well. These figures also remind us of the heavy burden of HIV infection on already overstretched health services.

In Abidjan, Projet Retro CI demonstrated that approximately 30% of all hospital deaths had HIV infection, and it was estimated that at least 18% of adult death in Abidjan in 1988 were associated with HIV (70).

Several papers at the Montreal conference pointed to the tremendous economic costs of HIV infection in the developed world. It appears that HIV infection has now become one of the leading causes of healthy life years lost per capita in urban populations in sub-Saharan Africa (71). This means that AIDS will probably have a negative impact on social and economic development in highly endemic countries.

CONCLUSION

It is increasingly clear that the epidemiology of HIV is becoming more heterogeneous and is constantly changing. The epidemic has not yet reached a stable situation in many populations. The identification of behavioral and biological risk factors for HIV infection is important for the control of this disease, because they may offer additional opportunities for intervention. A better knowledge of the natural history of HIV infection and of the interaction with other diseases should be useful for both patient management and resource allocation decisions.

The positive news is that the incidence of HIV infection and/or risk behavior is decreasing in various populations. This is not only demonstrated by

the spectacular decline of new infections in the homosexual community in many cities of the industrialized world, but perhaps also among some groups of prostitutes in the developing world. Encouraging data are also provided by a study in Kinshasa, which shows that married couples from a factory can cope with a moderate-sized HIV problem and remain married through an intensive counselling program (72). This also shows a potential role for employers in developing nations in providing such counselling. However, it is uncertain whether these results can be extrapolated to larger groups for whom such intensive counselling may not be feasible.

Humans can change their behavior at the political, scientific, and personal level. We can do better than the virus, because one important feature of humans is that we do not have to be as predictable as viruses. Complacency is one of the worst dangers when facing an epidemic since it would fundamentally threaten our ability to control the problem.

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