AIDS SPECIAL REPORT

AIDS in a New Millennium

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The AIDS pandemic has claimed more than 18 million lives since the disease was first described in the early 1980s (*1*). A new report (*2*) presenting the latest country-specific estimates of the pandemic has been released by the Joint United Nations Programme on HIV/AIDS (UNAIDS) in time for the 13th International Conference on AIDS to be held next week in Durban, South Africa. The report summarizes current knowledge of the pandemic's spread and impact, and provides the most up-to-date prevalence and mortality statistics for most countries. These grim statistics should propel us to take stock of the pandemic and to consider what must be done if its magnitude is to be reduced in the coming decade.

A Grim Picture . . .

Today, 34.3 million adults and children worldwide are estimated to be living with HIV (see Fig. 1). The pandemic is most severe in sub-Saharan Africa, which has 24.5 million people infected with HIV-1—almost 9% of the total adult population 15 to 49 years of age (see Fig. 2). The latest UNAIDS and WHO estimates show that in seven African countries—Botswana, Lesotho, Namibia, South Africa, Swaziland, Zambia, and Zimbabwe—more than one in five adults aged 15 to 49 now carry the virus (*2*). The prevalence of infection in Botswana is estimated to be about one-third of all adults. Simple prevalence statistics, however, cannot fully capture the impact of the pandemic. They do not include people who have already died of HIV/AIDS, or those who are not yet infected but surely will be. The cumulative probability of acquiring HIV throughout an individual's sexually active life is much higher than the "snapshot" provided by current HIV prevalence statistics. New analyses published in the UNAIDS report (*2*) indicate that in these seven African countries, at least two of every five girls and boys who are 15 years old today will die of AIDS, even given the optimistic scenario that the risk of HIV infection will be halved in the near future.

With the drastically increasing number of deaths seen in parts of the world where most HIV infections occur (see Fig. 1) but where access to life-prolonging treatments is negligible, it is painfully clear that HIV/AIDS is not just another infectious threat to health. HIV/AIDS is destroying the traditional fabric of societies and is a threat to all aspects of sustainable development. The classic population pyramid in developing countries will be radically changed by HIV/AIDS within the next two decades, as exemplified by projections for Botswana (see Fig. 3A) and as predicted by early studies of the demographic impact of HIV/AIDS (*3*). In contrast to the traditional population structure today, in 2020 there will be more women in their 60s and 70s than in their 40s and 50s (*4*). Never before has the world experienced death rates of this magnitude among young adults of both sexes and across all social strata. It is hard to imagine how societies will be able to cope with such dramatic changes, where the old will have to care for their children and grandchildren, and where young people will have to take responsibility for caring for family members at a much younger age than they do today. Although the pattern and severity of the pandemic is not as drastic in other continents as it is in Africa, it is of concern to all societies and will remain so for the foreseeable future.

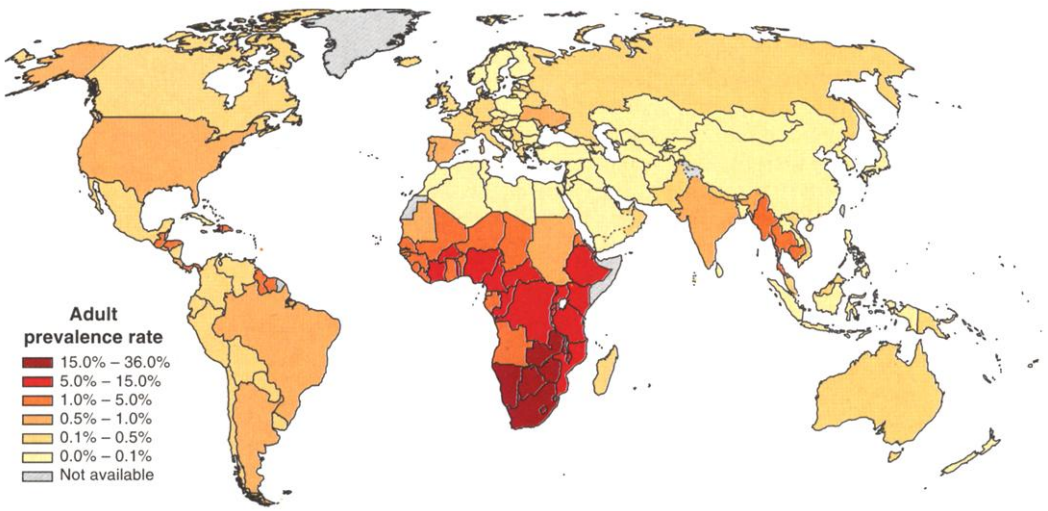

Fig. 1. Worldwide HIV prevalence rates in adults at the end of 1999. At the dawn of the new millennium there are 34.3 million adults and children living with HIV/AIDS. In 52 countries, more than 1% of all adults carry the virus. [Source: (*2*)]

In high-income countries, with constant vigilance and effective education of the young before they become sexually active, it should be possible to reduce the prevalence of HIV. Current prevalence statistics—ranging from 0.02% in Japan to 0.6% in the United States and 0.7% in Portugal—are low by comparison with sub-Saharan Africa, but they are still unacceptably high from a public health standpoint. The introduction of life-prolonging antiretroviral combination drug therapies in these countries has resulted in a drastic decrease in overall AIDS mortality since 1995. However, the increased survival time for those infected (leading to an increased pool of infected individuals) has many implications. These include the ever-present risk of enhanced transmission if treated individuals do not maintain safe sex practices and the growing cost of care and treatment of a constantly increasing number of infected persons over long time periods. The risk of treatment failure, often associated with poor adherence to drug regimens by patients, is always present because of the evolution of multi–drug-resistant viruses. Recent research (*5*, *6*) demonstrates that drug-resistant viruses are typically transmissible. Hence, to maintain recent gains in the life expectancy of infected patients on combination drug therapy, the importance of strict adherence to drug regimens must be stressed to both physicians and patients. The potential of HIV to evolve rapidly means that intense selection by widespread drug treatment will inevitably lead to the emergence of resistant virus strains. A new generation of antiretroviral drugs that induce fewer side effects and have longer half-lives in serum should help to combat this problem.

The transmissibility of HIV appears to

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be related to plasma viral load (*7*), and so effective antiviral treatment could reduce the rate at which new infections arise in populations with a moderate to high fraction of patients under treatment. To have a major impact, however, treatment must begin soon after infection and be maintained over very long periods. Because it is difficult to identify infections early and to manage adverse reactions to drugs over prolonged treatment periods, realistically it is unlikely that treatment can be used as a community-based intervention to reduce the spread of HIV. But safer drugs and better population-based screening programs could make this feasible in certain countries. As effective treatment becomes more widely available, its role in facilitating case finding and in providing counseling should be given greater prominence.

One downside of effective treatment is the tendency for increased risk behavior among treated individuals who believe they are no longer infectious, or among members of susceptible communities who fear infection less because it is treatable. Recent reports suggest that risk behavior is increasing again in some of the most affected communities in industrialized countries (*8, 9*). In San Francisco, for example, reported cases of rectal gonorrhea have more than doubled between 1993 and 1998 (from 20 per 100,000 population to 44 per 100,000). Concomitantly, reported risk behaviors such as multiple partners and unprotected anal sex increased substantially. A positive recent development is the demonstration that antiretroviral treatment of pregnant women in late-stage pregnancy has a significant impact on the rate of vertical transmission from mother to child. One such study in Bangkok showed a reduction in maternal transmission from 18.6% to 9.2% using a short course of zidovudine (*10*).

In the largest countries of Latin America and the Caribbean, AIDS has charted a similar course to the epidemic in North America. The spread of HIV has largely been concentrated among the most vulnerable populations, such as intravenous drug users and men who have sex with men, but infections through heterosexual intercourse are increasing. Indeed, in many of the smaller, poorer countries in this region, the spread of HIV has been much greater among heterosexuals. Haiti, with an overall HIV prevalence in adults of about 5%, is the worst affected country outside of Africa. However, there are 10 other countries in this region with an estimated adult prevalence of more than 1%.

In Asia, the picture is diverse and still unfolding. HIV prevalence exceeds 1% among 15- to 49-year-olds in Cambodia, Myanmar, and Thailand, but the prevalence is much lower in many of the populous nations within this region. In Indonesia, the world's fourth most populous country, it is estimated that fewer than 5 people in 10,000 are living with HIV. In the Philippines the rate is only slightly higher, at 7 per 10,000. These figures, however, do not tell the whole story. There are more people living in India alone (almost a billion) than in all of the sub-Saharan nations together, and many of the Indian states have larger populations than most African countries. Thus, the calculation of a nationwide average may be misleading. In India, where roughly 7 adults in 1000 are infected with HIV/AIDS, this means that around 3.7 million people are living with the virus. Some Indian states seem to have almost no HIV infections, but others (for example, Tamil Nadu and Maharashtra) have an adult HIV prevalence of 2% or more. In Manipur, about 2.2% of pregnant women tested positive for HIV in 1999, and in Mumbai prevalence among sex workers reached 71% in 1997. It is difficult to predict whether the epidemic will spread widely in those Asian regions where prevalence is low today, but it is not unlikely. Experience clearly shows that no society is immune to a widespread epidemic, and risk behaviors are prevalent and on the rise in many parts of Asia. In China, for example, an increase in sexually transmitted infections over the past few years suggests increasing potential for the spread of HIV. In 1964, the Chinese government declared that sexually transmitted infections had been eliminated through a series of major intervention campaigns. However, over the last decade the number of reported cases has been increasing steadily. Mass screening among rural and urban women in Yunnan Province between 1990 and 1996 showed rates as high as 0.9% and 16.2% for gonorrhea and trichomoniasis, respectively (*11*). The extent to which further spread occurs will be determined primarily by the level of effort that is put into prevention.

. . . With Glimmers of Hope

The UNAIDS report (*2*) does describe some success stories where intervention

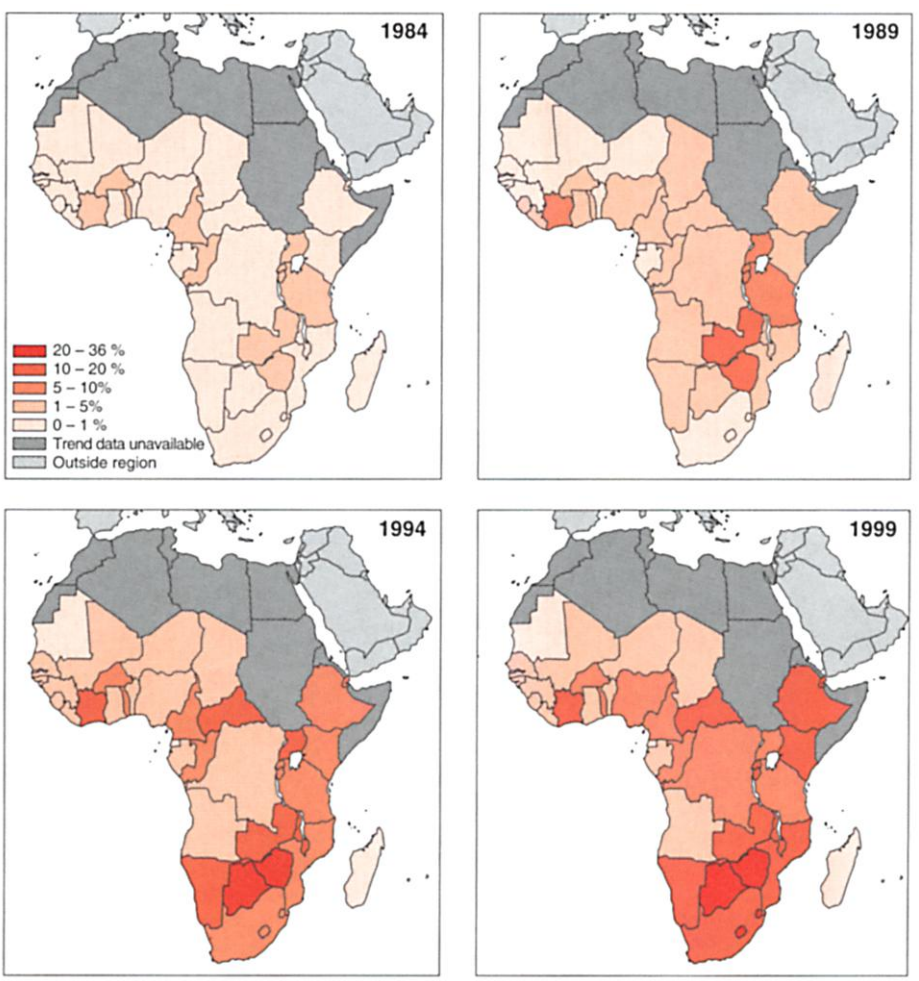

Fig. 2. The spread of HIV is most severe in sub-Saharan Africa. Although countries in West and Central Africa were among the first to be hit by HIV, more recently the virus has spread to countries in the Horn of Africa where the worst epidemics are now found. [Source: (*2*)]

has slowed the spread of HIV. Such cases should be interpreted cautiously because the natural dynamic of the epidemic is complex in the absence of intervention, involving one or more peaks in incidence [depending on the degree of mixing between the major at-risk groups (*12*)] followed by a slow decline to a stable endemic state. The whole pattern emerges on a slow time scale of many decades. All the well-documented success stories reflect a strong, committed, multi-sectorial response to the epidemic, as well as a willingness by government and community leaders to take difficult and often unpopular decisions. Examples include Uganda, where infection rates in young women 15 to 19 years of age started to decrease from about 30% in urban areas in the early 1990s to less than 10% in 1998 (*13*). Similar trends are now being seen in Zambia. An early and committed response in Senegal has kept prevalence low, at less than 1% of the adult population, in most parts of the country since the beginning of the epidemic. In Thailand, the "100% condom use campaign" (*14*) halted a potentially large-scale epidemic. In parts of Thailand, more than 10% of young men were HIV-positive in the early 1990s (*15*). Since then, levels of infection have declined steadily. Cambodia has launched a similar campaign building on the Thai experience, and initial results are promising. In the Indian state of Tamil Nadu, a strong response to HIV/AIDS has resulted in marked decreases in casual sex and increases in condom use in the groups at highest risk (*16*). In Australia, needle exchange and other programs for intravenous drug users were put in place early in the epidemic, leading to consistently low prevalence rates among this population (*17*). Early and concentrated collaborative efforts by governments and nongovernmental organizations in high-income countries have also led to drastic changes in behavior in the populations at highest risk. In the United States and some European countries, condom use in anal intercourse among men who have sex with men increased from virtually zero to 70% or more. Furthermore, early in the epidemic condoms became available in supermarkets, and machines selling syringes were installed in many European cities by the mid-1980s.

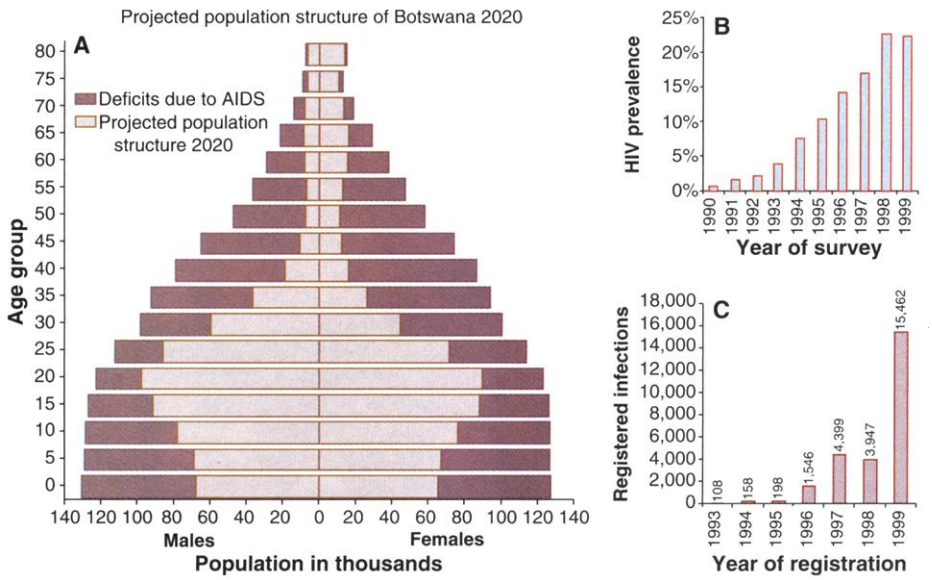

Fig. 3. (**A**) Projected population structure in Botswana in 2020. The population structure will change from the typical "age pyramid" into a chimney-shaped structure because of the HIV/AIDS epidemic. The sharp decrease in numbers of children reflects child mortality due to HIV/AIDS as well as a reduction in the number of live births due to adult mortality and reduced fertility in HIV infected women. [Source: (*4*)] (**B** and **C**) Increases in HIV infection in South Africa and Russia. In South Africa (**B**), nationwide prevalence rates in women attending antenatal clinics increased from less than 1% in 1990 to more than 20% a decade later, with prevalence rates of up to 1 in 3 women in the province of KwaZulu/Natal. [Source: Department of Health, South Africa, April 2000] Of the estimated 130,000 adults and children living with HIV/AIDS in Russia (**C**), about 20% were officially registered at the end of 1999. [Source: Russian Federal AIDS Centre, 2000]

Efforts Now for Benefits Later

Why is the HIV epidemic rapidly spreading in different communities throughout the world when we know how HIV is spread and how this can be prevented? How is it possible that in South Africa, HIV prevalence grew from 1% in 1990 to about 20% in the entire adult population less than 10 years later (see Fig. 3B)? In 1999, more HIV infections were diagnosed in Russia than in all previous years put together, due to a massive HIV epidemic among intravenous drug users in Moscow (see Fig. 3C).

Our understanding of AIDS and of the epidemiology and control of HIV are derived from interdisciplinary scientific study. But the societal and political response to the epidemic has not been commensurate with improvements in scientific understanding. Is this because the challenges of dealing with a silent epidemic are too great, is it our failure as scientists to communicate, or is it a lack of confidence on the part of many governments and communities in the guidance provided by scientific studies?

Since the discovery of the relationship between disease and microorganisms, and the subsequent emergence of the eras of antibiotics and vaccines, society has expected scientific research to lead inevitably to the development of "magic bullets" to either cure or protect against infection. For HIV/AIDS this would mean an effective cure induced by either chemotherapy or immunotherapy, or a protective vaccine. Despite the research achievements of the past two decades, neither of these options is available today. Most likely, they will not exist in the near future. Yet the vast majority of HIV infections could be prevented through simple changes in behavior, namely avoiding risky sex or avoiding the use of unsterile injection equipment. The likelihood of changes in behavior obviously depends on knowledge, the availability of commodities such as condoms and sterile needles, and the existence of a social and political environment that encourages and supports such changes.

The difficulties in mounting an effective response to HIV/AIDS are discussed in the new UNAIDS report and elsewhere (*18*). One critical element hampering an effective response is the fact that the epidemic is silent, in terms of overt disease and ultimately mortality, for many years. This gives ample time (decades) for denial to occur and for complacency to prosper. Unfortunately, the benefits of intervention programs will not be seen quickly because of the slow dynamic of the epidemic and the long average interval between infection and overt disease. This means that measures should be put in place when prevalence is low, long before the full impact of an uncontrolled epidemic is felt. Intervention programs must be planned on mid- and long-term time scales, with careful attention given to monitoring impact and evaluating effectiveness. Difficult and seemingly costly decisions need to be taken before the immediate pressures of high prevalence and mortality are felt. Leader-

ship is required with a long-term vision and with a willingness to learn from the successes and failures of others.

It is difficult to predict how the epidemic will develop in the future. We have seen unexpected successes, but also the dramatic spread of HIV to prevalence rates that few believed possible. Many of the countries where HIV prevalence is currently low have all of the ingredients for the extensive spread of HIV if no action is taken. In others, where significant spread has already occurred, prevalence may continue to rise until HIV endangers the entire society. The future course of the pandemic will depend largely on how the successes of today can fuel immediate action in many more countries and communities.

Research has provided a good scientific understanding of HIV and AIDS. Epidemiological and public health studies have provided clear guidance on what actions can control the pandemic. What remains is the political will to implement the programs necessary to stop HIV transmission, and the necessary resources to initiate and maintain an effective response. The international conference on AIDS in South Africa will bring together more than 10,000 researchers, public health specialists, activists, policy-makers, and decision-makers from governments and communities around the world. It is to be hoped that this exchange can at last bring a sense of real urgency to the need to respond to the disaster facing us from the AIDS pandemic. This response must be immediate, it must have a united political leadership from all governments, and it must be on a scale of resource allocation not seen before in the history of our fight against infectious disease.

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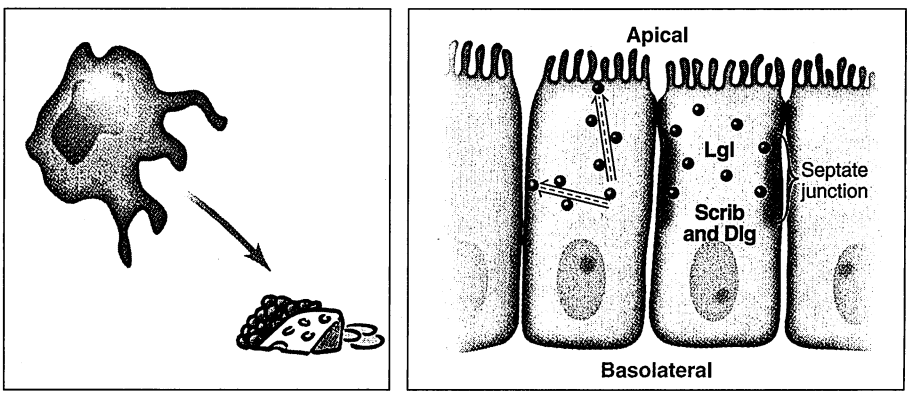
PERSPECTIVES: CELL BIOLOGY

Travel Bulletin—Traffic Jams Cause Tumors

Mark Peifer

As we depart on vacation, we're likely to get a crash course on what happens when traffic is not properly directed. The global transportation system is a marvel, carrying people and goods from Toledo to Timbuktu and all points between, but just try telling that to someone stuck in a traffic jam between Philadelphia and New York with three kids in a minivan. Just as the transportation system depends on the smooth operation of a complex mix of machinery and personnel, so the proper functioning of our bodies' cells—and ultimately of our bodies—depends on proper traffic direction. This travel advisory is well illustrated by the report from Bilder and colleagues on page 113 of this issue (*1*). The authors reveal surprising connections between three seemingly different cellular events: protein transport, cell polarity, and the regulation of cell proliferation.

Cells exist in an asymmetric environment, and their response to this environment requires that they are asymmetric as well. For example, even single cells must detect and move toward nutrients and away from predators. To achieve asymmetry cells are polarized, that is, different cellular machinery is deployed at distinct locations on the cell surface. Our understanding of the machinery that regulates cell polarity rests on twin experimental approaches: cell biology in cultured mammalian cells and genetics in the worm *Caenorhabditis elegans*, the fruit fly *Drosophila*, and yeast. Animal cell polarity has been most closely examined in epithelial cells, which have an apical-basal axis of polarity (that is, the top and bottom of the epithelial cells are different). The apical and basolateral domains of epithelial cells are arrayed with a different set of proteins; protein complexes at the lateral junctions between adjacent cells separate these two domains (see the figure). Although the establishment of cell polarity during development remains rather mysterious, the maintenance of cell polarity clearly depends on proper traffic direction—epithelial cells



Scribbling connections. All eukaryotic cells are polarized, with different proteins localized to distinct membrane domains. (**Right**) Epithelial cells accumulate different proteins on their apical (top) and basolateral (bottom) surfaces. Proteins are transported within the cell in vesicles that "move" along cytoskeletal highways. Different subsets of proteins are targeted to the apical and basolateral cell surfaces. Scrib and Dlg are localized at the septate junctions along the lateral cell surface, whereas Lgl coats vesicles that are found both in the cytoplasm and "docked" at the lateral surface of the cell.

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