

Yes, the agency is trying — but how effectively, and on whose behalf?

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One Disease, Two Epidemics — AIDS at 25

Kent A. Sepkowitz, M.D.

Twenty-five years have passed since the first cases of AIDS were recognized. During the first two decades, the epidemiology and clinical presentation of the disease were established, and potent antiviral therapies were developed — for use in patients who could afford them. The progress of the past five years has been less dramatic. Indeed, the most salient change was a widening of the gap between the haves and the have-nots, so that today a single virus is responsible for two distinct public health calamities.

Placed against the backdrop of the global AIDS epidemic, the AIDS-related problems in developed countries seem tame. Much current activity in high-income countries involves managing the predictable effects of any potent therapy — toxic effects and drug resistance — rather than scrambling to provide basic care. Of course, these problems are not trivial. After a decade of highly active antiretroviral therapy, the group of common side effects loosely called body-fat or metabolic abnormalities — lipodystrophy and lipoatrophy, diabetes, glucose intolerance and insulin resistance, and dyslipidemia —

still have no established remedy. Adjustment of the antiretroviral regimen, improvements in diet and exercise, and additional medications help some of the people some of the time. Yet management of the disease often remains inadequate, a limitation that chills enthusiasm for the early initiation of therapy. Current guidelines recommend that no treatment be

given to an asymptomatic person with a plasma human immunodeficiency virus (HIV) RNA concentration of less than 100,000 copies per milliliter, unless the CD4 cell count is below 200 per cubic millimeter.¹

At the same time, the rate of drug resistance among circulating HIV strains continues to increase: from approximately 5 per-

Worldwide Prevalence and Incidence of HIV Infection and AIDS and Related Mortality in 1995, 2000, and 2005.*			
Variable	1995	2000	2005
	<i>millions</i>		
No. of cases of HIV infection or AIDS			
Total	14.0–15.0	36.1	40.3
In women	7.0	16.4	17.5
In children	1.5	1.4	2.3
No. of new HIV infections			
Total	4.7	5.3	4.9
In women	NA	2.2	NA
In children	0.5	0.6	0.7
No. of deaths			
Total	2.3†	3.0	3.1
In women	NA	1.3	NA
In children	0.5†	0.5	0.6

* NA denotes not available.

† Mortality data are from 1997 and reportedly represent a 50 percent increase over the previous year.

cent in samples gathered before 1996 to at least 15 percent in isolates obtained between 1999 and 2003.² Patients should therefore undergo resistance testing before therapy is begun.

In the United States, approximately 1 million persons are living with HIV infection or AIDS, and 164,000 to 312,000 of them remain unaware of their infection.³ Experts hypothesize that most of the 40,000 new infections that occur annually in this country arise from contact with these undiagnosed persons. Given this likelihood, investigators have examined the potential benefit of routine screening, rather than testing of only those perceived to be at increased risk. This strategy appears to be as cost-effective as screening for colon, breast, or prostate cancer, and the availability of a rapid oral test has simplified broadscale testing.

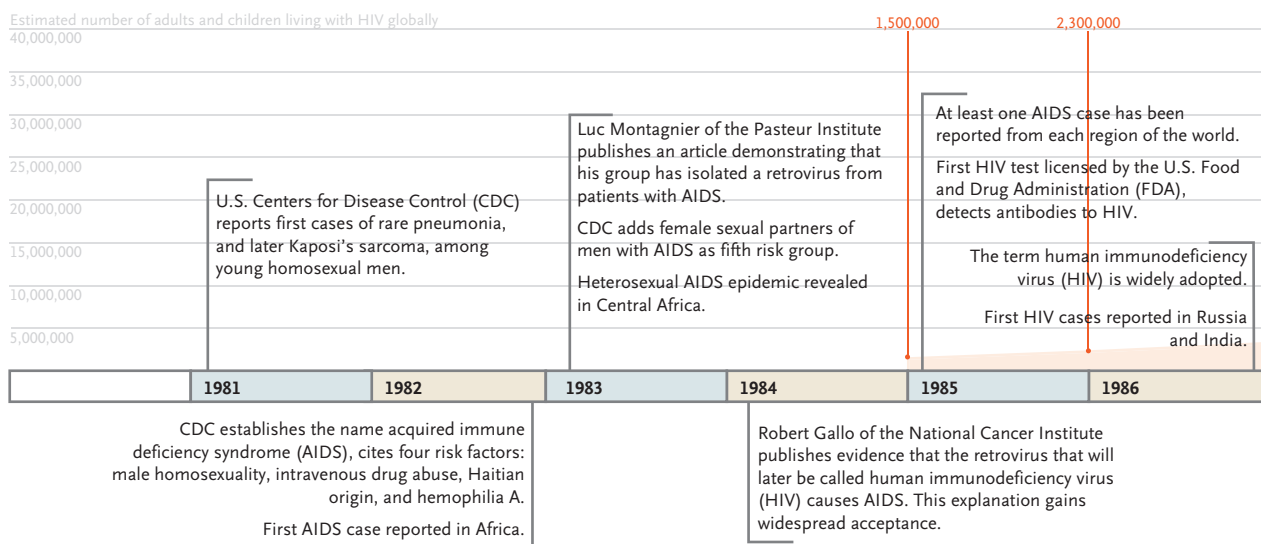
Some worry, however, that routine testing could erode patient confidentiality by circumventing safeguards that were erected in the 1980s, when HIV infection seemed to be untreatable and universally fatal. Current debate focuses on

whether these once-crucial laws paradoxically now impede the public health response to the epidemic by encumbering the testing process.

For those who have already tested positive, treatment has become more convenient but not more potent in the past five years, with the introduction of numerous once-daily dosing regimens. Enfuvirtide, the first fusion inhibitor, is effective in many persons with highly resistant virus, but twice-daily injections are difficult for some to sustain.¹ The possibility that tenofovir, with or without emtricitabine, may be effective as prophylaxis has received attention on two different fronts. The first was a description of its frequent use as a “party” pill by uninfected persons who planned to engage in high-risk activity. The second was more recent studies showing that its use in high-risk populations reduces the infection rate. This approach, however, may accelerate the emergence of drug resistance and thereby compromise the effectiveness of the prophylactic or therapeutic use of these medications.

Meanwhile, the second epidemic — in low- and middle-income countries — has grown far vaster than that in the United States, as HIV continues its nightmarish expansion (see table). Only one fifth of people in developing countries who need treatment are receiving antiretroviral therapy.⁴

The establishment of cheap, effective approaches to prevention has been similarly elusive. Until a vaccine is developed, prevention must continue to rely on more complicated and probably less useful options. The effect of male circumcision on HIV transmission remains controversial, despite a report from South Africa, where more than 3000 men were randomly assigned to undergo either circumcision or observation.⁵ The trial was stopped early because of a 61 percent reduction in the rate of new infections in the circumcision group that persisted after researchers had controlled for differences in sexual behavior, condom use, and health care-seeking behavior. The response to this study, however, remains wary and even dismissive, a hesitance that seems misplaced, given the role



of HIV in forcing frank discussions of sexual activity.

Two long-considered prevention strategies appear to be ready for definitive clinical trials. Although monthly azithromycin given to prevent genital ulcer disease did not reduce the risk of HIV transmission, long-term antiviral therapy for genital herpes simplex — a tactic that may have a better biologic foundation — is now being examined. Similarly, studies of microbicides are finally advancing.

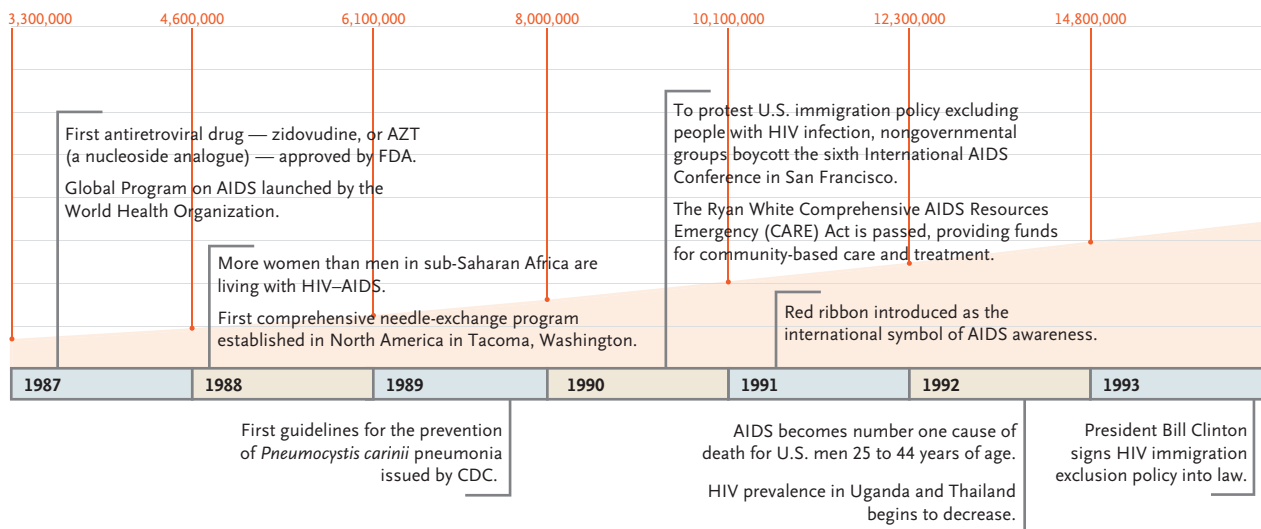
The provision of clean disposable needles for health care and the maintenance of a safe blood supply were high priorities for the United States in the 1980s. The cost of establishing similar programs in resource-poor countries is daunting, yet the risk of HIV transmission by either route is substantial — perhaps higher than the risk from sexual contact. Currently, because of its cost, only 30 percent of countries routinely screen blood. Screening potential donors is a cheaper approach, yet it may rely on the race-based exclusion of donors, creating a different dilemma.

Another concern has been the powerful reciprocal interactions between HIV and *Mycobacterium tuberculosis*. Although these interactions were demonstrated by outbreaks of multidrug-resistant tuberculosis in the United States 15 years ago, the devastation caused by these intertwined epidemics continues to startle. Tuberculosis kills as many as one of every seven people with AIDS worldwide, and one third of the increase in cases of tuberculosis over the past five years can be attributed to the HIV epidemic.

Control of tuberculosis in areas where HIV is endemic is complicated by several factors, including a growing fear of acquiring tuberculosis that makes some health care workers reluctant to care for those infected with HIV. A lone optimistic note has been the increasing interest in applying a tool that helped to tame tuberculosis in some countries — directly observed therapy — to the treatment of HIV infection. If effective, this tactic may preserve both individual health and the drug susceptibility of circulating virus.

It is unfortunate that for the past 25 years, the lessons learned about HIV prevention and control in one country have failed to inform decisions in others. As a result, the world has witnessed a slow-motion domino effect, as the disease overwhelms country after country. Typically, locals place the blame on foreigners and foreign behavior — just as the French once called syphilis “the Italian disease” and the Italians considered it “the French disease.” This sort of buck passing has delayed the control of AIDS in every country. By the time the scale of the problem is finally appreciated, a mature epidemic is in place, and the cost in lives and money has increased exponentially.

We can only hope that the years ahead will be characterized not just by better drugs, new vaccines, and improved prevention methods, but also by the adoption of the humility necessary to control a disease that is transmitted through sexual activity and drug use — two of proper society’s least favorite topics. The prime mover of the epidemic is not inadequate anti-retroviral medications, poverty, or



bad luck, but our inability to accept the gothic dimensions of a disease that is transmitted sexually. Only when we cease to dodge this fact will effective HIV-control programs be established. Until then, it is no exaggeration to say that our polite behavior is killing us.

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The HIV–AIDS Pandemic at 25 — The Global Response

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On June 5, 1981, when the Centers for Disease Control reported five cases of *Pneumocystis carinii* pneumonia in young homosexual men in Los Angeles,¹ few suspected it heralded a pandemic of AIDS. In 1983, a retrovirus (later named the human immunodeficiency virus, or HIV) was isolated from a patient with AIDS. In the 25 years since the first report, more than 65 million persons have been infected with HIV, and more than 25 million have died of AIDS. Worldwide, more than 40 percent of new infections among

adults are in young people 15 to 24 years of age.²

Ninety-five percent of these infections and deaths have occurred in developing countries. Sub-Saharan Africa is home to almost 64 percent of the estimated 38.6 million persons living with HIV infection (see Figure 1). In this region, women represent 60 percent of those infected and 77 percent of newly infected persons 15 to 24 years of age.²

AIDS is now the leading cause of premature death among people 15 to 59 years of age. In the

hardest-hit countries, the foundations of society, governance, and national security are eroding, stretching safety nets to the breaking point, with social and economic repercussions that will span generations.

This crisis demanded a unique and truly global response to meld the resources, political power, and technical capacity of wealthy countries with the needs and capacities of developing countries. Such a response would have required policymakers to address taboos concerning sexual behavior, drug use,

