REVIEW ARTICLE

GLOBAL HEALTH

Response to the AIDS Pandemic — A Global Health Model

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JUST OVER THREE DECADES AGO, A NEW OUTBREAK OF OPPORTUNISTIC INfections and Kaposi's sarcoma was reported in a small number of homosexual men in California and New York.[1,2] This universally fatal disease, which was eventually called the acquired immunodeficiency syndrome (AIDS), was associated with a complete loss of CD4+ T cells. Within the first year of its description, the disease was also identified in patients with hemophilia, users of injection drugs, blood-transfusion recipients, and infants born to affected mothers. Soon thereafter, a heterosexual epidemic of AIDS was reported in Central Africa, preferentially affecting women.[3,4] Little did we know at the time that this small number of cases would eventually mushroom into tens of millions of cases, becoming one of the greatest pandemics of modern times.

Within 2 years after the initial reports of AIDS, a retrovirus, later called the human immunodeficiency virus (HIV), was identified as the cause of AIDS.[5] Diagnostic tests were developed to protect the blood supply and to identify those infected. Additional prevention measures were implemented, including risk-reduction programs, counseling and testing, condom distribution, and needle-exchange programs. However, HIV continued to spread, infecting 10 million persons within the first decade after its identification.

An interactive graphic including a prevalence map, a timeline, and details of HIV structure and life cycle is available at NEJM.org

The second decade of AIDS was marked by further intensification of the epidemic in other areas of the world, including the southern cone of Africa, which saw an explosive HIV epidemic. Asia and the countries of the former Soviet Union also reported a marked increase in the spread of HIV. However, by the mid-1990s, with the discovery of highly active antiretroviral therapy, rates of death in developed countries started to decline. The use of antiretroviral drugs during pregnancy also resulted in a substantial decline in mother-to-child transmission of HIV in high-income countries. However, without access to antiretroviral drugs in low- and middle-income countries, rates of death and mother-to-child transmission continued to increase, with 2.4 million deaths and more than 3 million new infections reported in 2001. Of these new infections, two thirds occurred in sub-Saharan Africa.[6]

INTERNATIONAL RESPONSE TO AIDS — A GLOBAL HEALTH MODEL

It was not until the third decade of the epidemic that the world's public health officials, community leaders, and politicians united to combat AIDS. In 2001, the United Nations General Assembly endorsed a historic Declaration of Commitment on HIV/AIDS, a commitment that was renewed in 2011.[7] These actions resulted in the formation of the Global Fund to Fight AIDS, Tuberculosis, and Malaria, which was established to finance anti-AIDS activities in developing countries. In 2003, President George W. Bush announced the President's Emergency Plan for AIDS

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Relief (PEPFAR), which allocated billions of dollars to the countries hardest hit by AIDS.

This unprecedented global response to the AIDS pandemic can serve as a model for the response to other global health threats. For example, the global AIDS response incorporated a multisectoral approach that involved public health officials, clinicians, politicians, and leaders in civil society, business and labor, the armed forces, and the law, working in concert and with financial resources in excess of $15 billion per year[8] to reduce the incidence of HIV infection and associated mortality. The response to the pandemic required a coordinated global effort, which has been led by the Joint United Nations Program on HIV/AIDS (UNAIDS) since 1996. This transformational response helped redefine what is meant by health diplomacy and led to a new culture of accountability in international development. Tiered pricing of medicines became commonplace, and renewed optimism provided a boost for research on other neglected global health issues. This response to the AIDS pandemic highlighted the shortage of health care workers, inadequate availability of essential medications, and weaknesses in primary health care and public health systems. The stigma of HIV infection and inequities in the care of those infected focused attention on social and medical equity and human rights.

Although it has been argued that the provision of health care for patients with other conditions may have suffered from "vertical" AIDS programs (i.e., programs focused exclusively on AIDS), especially because of their recruitment of scarce health care workers,[9] there is also evidence that the AIDS response has had multiple collateral benefits, including a major increase in attention to and funding for global health issues, particularly malaria and tuberculosis, and a strengthening of services for maternal and child health in some countries.[10-12] The unified and integrated response to AIDS, although far from perfect, can serve as a model for society's future response to the growing epidemic of chronic diseases, obesity, and injuries, along with maternal and child health.[13]

THE FOURTH DECADE OF AIDS

UNAIDS estimates that in 2011, a total of 34.2 million persons were living with HIV infection, as compared with 29.1 million in 2001; 2.5 million persons were newly infected in 2011, a 22% decline from the number in 2001, and 1.7 million died, a decline of 26% from 2005, when the number of AIDS deaths peaked at 2.3 million.[8,14] Similarly, the number of new infections among neonates and infants decreased from a peak of 570,000 in 2003 to 330,000 in 2011 as a result of interventions to prevent mother-to-child transmission.

However, these global figures hide a wide diversity. Figure 1 shows the prevalence of HIV infection among adults according to country, with sub-Saharan Africa continuing to be the most affected continent, followed by Eastern Europe and the Caribbean.[15] A special case is southern Africa, where HIV infection has become hyperendemic, with an overall prevalence among adults of up to 31% in Swaziland, 25% in Botswana, and 17% in South Africa. In Swaziland, the prevalence among women between the ages of 30 and 34 years is an astonishing 54%.[7] Even within a country, the prevalence of HIV infection varies widely according to region and risk group. In 2010, the prevalence of antenatal HIV infection in South Africa ranged from 18.4% in the Northern Cape province to 39.5% in KwaZulu Natal.[16] Men who have sex with men, female sex workers, users of injection drugs, truck drivers, fishermen, and military personnel are disproportionately affected around the world.[17-22]

There is also heterogeneity in epidemiologic trends. Whereas the spread of HIV infection is slowing in most regions, the incidence of infection continues to increase in Eastern Europe and several Asian countries.[14] There is also a resurgence of HIV infection caused by increased risk behavior among men who have sex with men in several European cities — for example, a reported 68% increase in sexual risk behavior among such men in Amsterdam[23] — in spite of high rates of HIV testing and access to antiretroviral therapy. At the same time, HIV infection is spreading to previously unaffected populations, such as injection-drug users in parts of Africa and men who have sex with men across Asia and Africa, where widespread homophobia drives these men underground.

PROGRESS IN TREATMENT OF HIV INFECTION

Twenty-six antiretroviral drugs have been licensed for the treatment of HIV infection. The availability of these drugs led to reductions in

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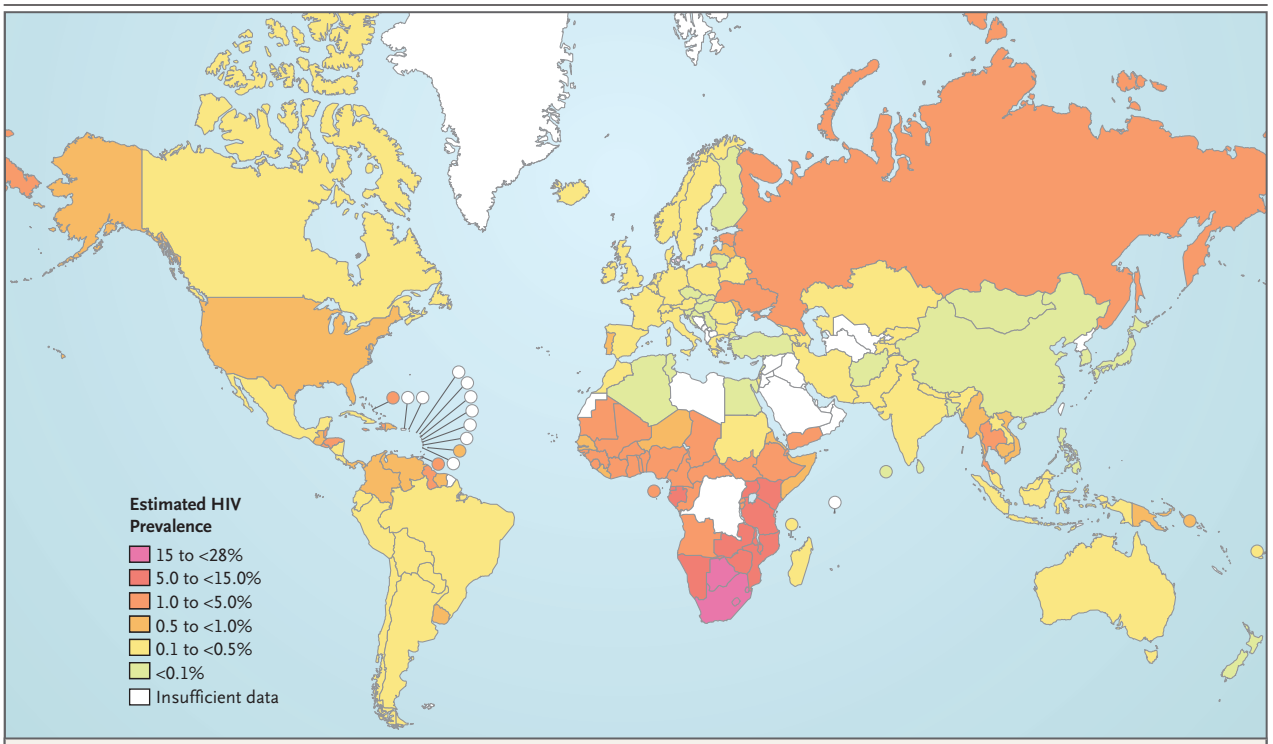

Figure 1. World Map of Prevalence of HIV Infection.
Data are from UNAIDS,[15] UNICEF (www.unicef.org), and the World Bank (www.worldbank.org). An interactive version of this map is available at NEJM.org.

mortality starting in the late 1990s in the United States and Europe. Subsequent reductions in the cost of antiretroviral therapy, the availability of generic antiretroviral drugs, and increases in international financial aid led to a marked expansion in drug availability. As a result, the number of persons receiving antiretroviral therapy in low- and middle-income countries rose from less than 200,000 persons in 2001 to 8 million persons in 2011[14] (Fig. 2). In addition, the death rates in some of the hardest-hit countries have started to decline.[24]

With the life expectancy of a patient with HIV infection receiving treatment approaching that of a person without HIV infection,[25,26] there has been an increased emphasis on starting antiretroviral therapy as early as possible in the course of infection. The revised 2012 guidelines of the U.S. Department of Health and Human Services recommend the initiation of antiretroviral therapy in all persons with HIV infection.[27] These recommendations are based on evidence regarding the association between ongoing HIV replication and disease progression. In addition, because the use of antiretroviral therapy prevents the transmission of HIV in discordant couples (i.e., in which one person is infected and the other is not),[28] the guidelines recommend that such therapy be offered to all patients with HIV infection in order to reduce the risk for their sexual partners.

At variance with the U.S. and European guidelines,[29] World Health Organization guidelines continue to recommend the initiation of antiretroviral therapy in all persons with CD4 counts of 350 per cubic millimeter or less, with recognition of the limitations of cost and availability in many countries.[30] However, all guidelines strongly recommend antiretroviral therapy for all infected persons (regardless of the CD4 count) who are pregnant or who have a history of an AIDS-defining illness, tuberculosis, or coinfection with hepatitis B virus. The guidelines were recently updated to recommend antiretroviral therapy for HIV-discordant couples[31] (Table 1).

Despite advances in the accessibility of antiretroviral therapy, many challenges remain in

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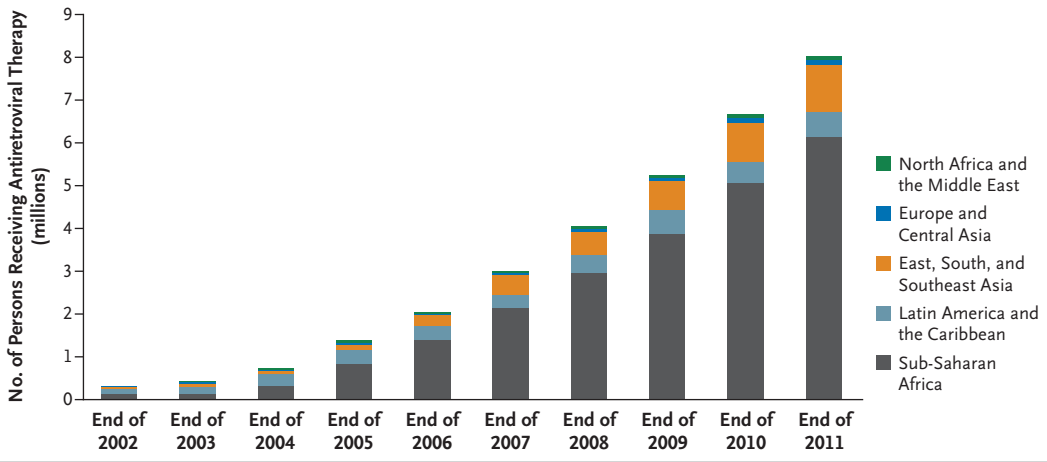

Figure 2. Number of Persons Receiving Antiretroviral Therapy in Low- and Middle-Income Countries, According to Region (2002–2011).

Data are from UNAIDS.[14]

the provision of care for persons with HIV infection. In the United States, the Centers for Disease Control and Prevention estimates that 1.2 million persons were living with HIV infection in 2008; of these persons, only 28% ultimately had suppressed viral levels, meaning that a majority were infectious owing to an insufficient uptake of testing, access to antiretroviral therapy, and adherence to therapy.[32-34] In one study in Mozambique involving 7005 persons with HIV infection, only half were enrolled in programs providing care, and only a small proportion ultimately started antiretroviral therapy and maintained adherence to the regimen at a rate of more than 90% for more than 180 days[35] (Fig. 3). These numbers reflect insufficient access and adherence to treatment that are mostly due to an inconsistent pattern of diagnosis, linkage to care, use of the CD4 count as a threshold for the initiation of therapy, and retention in care. In sub-Saharan Africa, the proportion of the population that is being tested for HIV remains low. In low- and middle-income countries, the average CD4 count at the time of initiation of antiretroviral therapy remains low, with a median of 124 cells per cubic millimeter.[36] Intensified efforts are needed to identify persons who are infected, initiate therapy with standardized effective regimens, and encourage adherence to the regimen and retention in the program of care. Only with success at each stage in the continuum of care can the ultimate goals of improving health, extending lives, and preventing further HIV transmission be achieved.

EVOLUTION OF PREVENTION STRATEGIES

A reduction in the incidence of HIV infection has been a top priority for AIDS control. The initial prevention strategy was based on behavioral change: abstinence, fidelity to a single partner, and use of a condom. This strategy met with only limited success, with Thailand's 100% condom campaign and Uganda's initial AIDS response being exceptions.[37,38] There is growing evidence that the relative decline of more than 25% in the incidence of HIV infection from 2000 through 2010 in several African countries is the result of behavioral change.[39] The rate of condom use continues to increase, with several countries (including South Africa, India, and Botswana) reporting a rate of condom use of more than 75% during high-risk sexual intercourse.[6] However, condom use is still low in many other countries. A cause for concern is the finding that in several African countries (e.g., Uganda, Rwanda, and Zimbabwe), the number of men and women reporting multiple partners was higher in 2011 than the number 5 to 10 years earlier.[14]

Among injection-drug users, access to sterile injection equipment and drug-substitution ther-

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Table 1. Guidelines for the Initiation of Antiretroviral Drugs in Adults with HIV Infection.*

Clinical Condition or CD4 Count	Recommendations to Start Treatment		
	DHHS 2013[27]	EACS 2012[29]	WHO 2010[30,31]†
CD4 count			
≤350 cells/mm³	Yes (AI)	Yes	Yes
>350–500 cells/mm³	Yes (AII)	Asymptomatic patients, consider therapy; symptomatic patients, yes	Stage 1 or 2, defer therapy; stage 3 or 4, yes
>500 cells/mm³	Yes (BIII)	Asymptomatic patients, defer therapy; symptomatic patients, yes	Stage 1 or 2, defer therapy; stage 3 or 4, yes
Pregnancy	Yes (AI)	Yes	Yes
History of AIDS-defining illness	Yes (AI)	Yes	Yes
HIV-associated nephropathy	Yes (AII)	Yes	Yes
Coinfection with tuberculosis	Yes (AII)	Yes	Yes
Coinfection with HBV	Yes (AII)	Yes, when treatment is indicated for HBV; defer therapy if HBV infection does not require treatment and CD4 count is >500 cells/mm³; consider therapy if CD4 count is 350–500 cells/mm³	Yes, when treatment is indicated for HBV infection
Coinfection with hepatitis C virus	Yes (BII)	Yes, if CD4 count is <500 cells/mm³; defer or consider therapy if CD4 count is ≥500 cells/mm³	Not specified
Risk of transmission			
Perinatal transmission	Yes (AI)	Yes	Yes
Heterosexual transmission	Yes (AI)	Strongly consider	Yes
Other sexual-transmission risk groups	Yes (AIII)	Strongly consider	Not specified
Preferred combination regimens			
Patients receiving first-time therapy	Tenofovir and emtricitabine,‡ plus one of the following: efavirenz (AI), ritonavir-boosted atazanavir (AI), ritonavir-boosted darunavir (AI), or raltegravir (AI)	Tenofovir and emtricitabine‡ or abacavir and lamivudine, plus one of the following: nevirapine, efavirenz, rilpivirine; ritonavir-boosted atazanavir, darunavir, or lopinavir; or raltegravir	Zidovudine or tenofovir, plus lamivudine or emtricitabine, plus efavirenz or nevirapine
Coinfection with tuberculosis§	Regimens listed above	Tenofovir and emtricitabine,‡ plus either efavirenz or ritonavir-boosted protease inhibitor, plus rifabutin	Zidovudine or tenofovir, plus lamivudine or emtricitabine, plus efavirenz
Coinfection with HBV	Tenofovir and emtricitabine,‡ plus efavirenz (AI) or regimens listed above	Tenofovir plus emtricitabine,‡ plus efavirenz or same regimens as those for all patients	Tenofovir and emtricitabine,‡ plus efavirenz
Pregnancy	Zidovudine and lamivudine, plus ritonavir-boosted atazanavir or lopinavir (AI)	Zidovudine and lamivudine, plus ritonavir-boosted lopinavir, saquinavir, or atazanavir	Zidovudine and lamivudine plus nevirapine

* Recommendations are rated as follows: A, strong; B, moderate; and C, optional. Evidence is rated as follows: I, data from randomized, controlled trials; II, data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; and III, expert opinion. DHHS denotes Department of Health and Human Services, EACS European AIDS Clinical Society, HBV hepatitis B virus, and WHO World Health Organization.

† WHO stages include the following symptoms: stage 1, asymptomatic with generalized lymphadenopathy; stage 2, moderate weight loss, recurrent respiratory and oral infections, and herpes zoster; stage 3, severe weight loss, chronic diarrhea, thrush, severe bacterial infections, and tuberculosis within the past 2 years; stage 4, opportunistic infections, HIV wasting syndrome, and HIV encephalopathy.

‡ Lamivudine can be used instead of emtricitabine and vice versa.

§ In patients with HIV infection and tuberculosis, antiretroviral therapy should be started within 2 weeks after the initiation of treatment for tuberculosis if the CD4 count is less than 50 cells per cubic millimeter (AI). For patients with a CD4 count of 50 cells or more per cubic millimeter, therapy can be delayed beyond 2 weeks. The dose of antiretroviral therapy should be adjusted when used in combination with rifampin or rifabutin.

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apy (referred to as harm reduction) is highly effective in reducing the spread of HIV infection.[40] Yet several countries in Eastern Europe and Asia in which HIV epidemics are driven by injection-drug use continue to use ineffective, punitive approaches. The result is a sustained high incidence of HIV infection, which also feeds the sexual spread of HIV.[41] Structural approaches,[42] such as programs to reduce violence against women[43] and the use of cash transfers (i.e., cash payments that can be used for food purchases, transportation, education, health care, or other expenses) among adolescent school girls in Malawi,[44] should be integrated more widely into HIV-prevention agendas. In addition, laws that drive men with same-sex partners underground or prohibit harm reduction for injection-drug users can be major obstacles to effective HIV prevention.[17] That such laws can be reversed was illustrated in India, where same-sex relations were decriminalized in 2009.

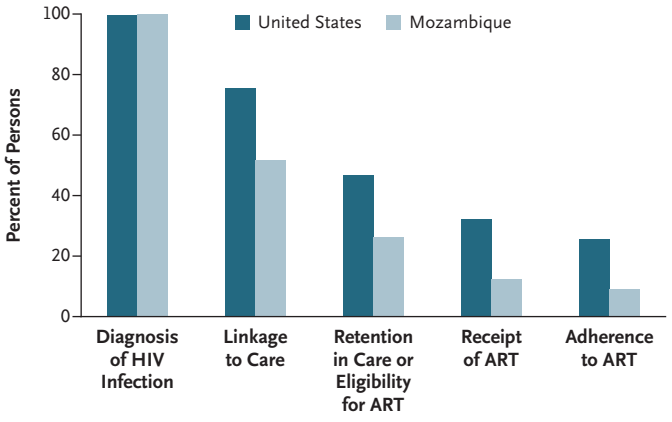

Figure 3. Factors Involved in the Diagnosis, Access to Care, Retention, and Treatment of HIV Infection in the United States and Mozambique.

Data for the United States are derived from Gardner et al.,[33] and data for Mozambique are derived from Micek et al.[35] Data for adherence to antiretroviral therapy for the United States represent the proportion of persons with viral suppression, whereas for Mozambique, the data represent the proportion of persons with adherence to antiretroviral therapy, according to responses on questionnaires and pill counts among persons who were retained in care for more than 1 year (since viral levels were not obtained).

BIOMEDICAL ADVANCES IN PREVENTION

MALE CIRCUMCISION

The first major biomedical breakthrough in prevention was the finding of reduced susceptibility to HIV infection among circumcised men, with an efficacy rate of 50 to 60% shown in three clinical trials.[45-47] Three years after the completion of the circumcision trial in Rakai, Uganda, high rates of community effectiveness (73%) in decreasing the incidence of HIV infection have been reported.[48] With an estimated cost per infection averted in the range of $150 to $900 over a 10-year period (depending on the local incidence of HIV infection), male circumcision appears to be one of the most cost-effective preventive approaches, requiring only a one-time intervention.[49]

PREEXPOSURE PROPHYLAXIS

Preexposure prophylaxis (i.e., the use of antiretroviral therapy before sex) with 1% tenofovir gel was reported to reduce HIV acquisition by 39% in women.[50] Daily use of oral combination prophylaxis with tenofovir and emtricitabine among HIV-negative homosexual men who had multiple partners reduced HIV acquisition by 44%.[51] In both studies, greater efficacy was observed among persons who had high levels of adherence to the medication regimen. Daily use of tenofovir or tenofovir plus emtricitabine reduced HIV acquisition by 66% and 73%, respectively, among unaffected partners in HIV-discordant couples[52] and among young heterosexuals in Botswana.[53] Although these findings are encouraging, two studies had conflicting results, with findings of no efficacy for either oral or gel tenofovir.[54,55] Such discrepancies in results may be due to low adherence to the drug regimens or differences in mucosal penetration. Recently, the Food and Drug Administration approved the daily use of oral emtricitabine and tenofovir disoproxil fumarate (Truvada, Gilead Sciences) for preexposure prophylaxis in combination with safer sex practices to reduce the risk of sexually acquired HIV infection among adults at high risk.

TREATMENT AS PREVENTION

Viral load is the single greatest risk factor for all modes of HIV transmission,[56] and treatment as prevention is based on the fact that antiretroviral therapy can reduce plasma and genital viral loads to undetectable levels, thereby reducing infectiousness.[28] This principle was first proved for the prevention of mother-to-child transmission[57] and was subsequently proved for the prevention

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of sexual transmission among discordant couples, with a reduction of 96% in the transmission rate.[28] This shift in focus from the use of antiretroviral agents for the treatment of HIV infection to their prophylactic use for the elimination of viral transmission has inspired optimism for achieving the goal of an AIDS-free generation.

COMBINATION PREVENTION

There is consensus that no single intervention can stop the spread of HIV and that combination prevention is the best approach.[58] Effective biomedical interventions coupled with behavioral and structural approaches may now successfully reduce the incidence of HIV infection to very low levels and ultimately control the epidemic. There is also a need to test in randomized trials the efficacy of treatment as prevention at the population level and to determine the optimal program design (in combination with specific preventive interventions), as well as ensuring good treatment coverage for persons in immediate need of clinical treatment.

From the perspectives of both efficacy and cost-effectiveness, HIV prevention should focus on populations at highest risk for transmission and should be customized to a wider range of realities than is currently the case. All components of combination prevention require some form of behavioral intervention, including adherence to condom use, antiretroviral-based prevention, and prevention of behaviors associated with an increased risk of infection. However, even when the most effective HIV interventions are used, most mathematical models suggest that by 2031 — 50 years after the identification of AIDS — there may still be as many as 1 million new infections globally every year.[59,60] Although a vaccination trial in Thailand showed an efficacy of 31%, providing a much-needed boost to vaccine research,[61] the search for such effective prophylaxis still eludes investigators.

THE CHALLENGES AHEAD

After 30 years of the AIDS epidemic, more than 34 million persons are still living with HIV infection worldwide, and the global response will clearly have to be sustained for at least several decades. An impressive array of evidence-based interventions can be implemented to treat established infections and prevent new ones. Studies of high-risk populations have shown that HIV infection can be prevented even in the most challenging settings. Nevertheless, UNAIDS reports that only 60% of sex workers, 46% of injection-drug users, and 40% of men who have sex with men were reached by HIV-prevention programs in 2008, and the incidence of HIV infection is rising again in several countries, including Uganda.[8,14]

In 2011, less than 25% of all persons with HIV infection had access to antiretroviral therapy or had virologic suppression from receipt of such therapy.[14] To ensure access to antiretroviral drugs, many lower-income countries are still almost entirely dependent on international aid, which has declined in recent years. As a result of successful therapy and increased life expectancy, we are witnessing an increase in the need for care for chronic diseases among persons with HIV infection. Thus, we need to develop innovative solutions for care delivery, including shifting specific tasks to health workers aside from clinicians and integrated service delivery in the community.

In conclusion, great progress has been made in the global response to the AIDS epidemic, but these achievements are fragile because of the enormous challenge of sustaining political, programmatic, and technical commitment, along with national and international funding. A certain level of AIDS fatigue on the part of funders and public health and political leaders coincides with the unprecedented opportunities for using new tools to control AIDS. Prevention and care now need to be targeted strategically, and creative combinations of behavioral, biomedical, and structural interventions need to be widely implemented.[59,60] These programs will require universal access, large-scale implementation, careful monitoring and evaluation, financial and technical resources, and robust commitment. Only then may we begin to see a substantial effect on the global spread of HIV infection.

No potential conflict of interest relevant to this article was reported.

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