Setting the Stage: Current State of Affairs and Major Challenges

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The global human immunodeficiency virus (HIV) pandemic reached staggering proportions over the past 2 decades, particularly in areas of sub-Saharan Africa and other developing countries. Tremendous increases in donor resources over the past decade have allowed for a rapid scale-up of antiretroviral treatment and greater access to basic care and prevention programs in countries worst affected by HIV infection and AIDS. These programs have had a tremendous impact on the lives of millions of individuals and have also created optimism and hope where previously there was despair. Major challenges remain in combating the current HIV pandemic with regard to access to treatment; efficiency, quality, and sustainability of current programs; and the scale-up of evidence-based, effective prevention strategies. The global health community and political leaders will need to overcome these challenges if a long-term effective response to the HIV pandemic is to be achieved.

SCOPE OF THE EPIDEMIC

Over the past 28 years, the human immunodeficiency virus (HIV) pandemic has spread to all areas of the world, and HIV infection continues to be associated with high rates of morbidity and mortality, particularly in developing countries. In 2007, the United Nations Joint Programme on HIV/AIDS estimated that there were 33 million persons with HIV infection and 2.7 million new infections [1]. Although the percentage of individuals with HIV infection has stabilized, the overall number of persons with HIV infection has steadily increased as new infections occur each year, treatments for HIV infection extend life, and new infections outnumber AIDS-related deaths. Regionally, southern Africa continues to have a disproportionate share of the global burden of HIV infection, with 35% of the world’s new HIV infections and 38% of AIDS-related deaths annually. Two-thirds of all persons with HIV infection and 60% of all women with HIV infection live in sub-Saharan Africa. Asia and Eastern Europe combined account for an additional 20% of persons infected with HIV, which illustrates the rapid growth of the epidemic in those countries. Even in the United States, new estimates from the Centers for Disease Control and Prevention suggest that >1.0 million persons are infected with HIV, and a stable continuous epidemic of >56,000 new infections has been occurring each year for the past 10 years [2, 3]. In the District of Columbia, more cases of AIDS were reported per 100,000 population in 2006 than were reported in many African countries [4]. In summary, the HIV and AIDS pandemic is well established in every country, with some variations in intensity, modes of transmission, and access to treatment and prevention.

As a result of the global HIV epidemic, life expectancy has been reduced by >20 years in countries most heavily affected, slowing economic growth and exacerbating household poverty [1]. As a consequence, the HIV epidemic has mobilized a tremendous political, financial, and human resource response and has focused the world on important global health disparities. Millennium Development Goal 6 was embraced in 2000 to halt and begin to reverse the global HIV epidemic by 2015. The massive increase in financial resources for HIV-related activities in countries worst affected by HIV infection and AIDS is beginning to yield results, although many challenges endure. The annual number...
of AIDS-related deaths has decreased in recent years from 2.2 million in 2005 to 2.0 million in 2007. Progress has definitely been made in prevention, treatment, and care over the past decade, but several challenges remain that threaten the ability to achieve universal access by 2010 and Millennium Development Goal 6 by 2015. The epidemic remains staggering in proportion, despite enormous progress that is being made in access to care and prevention in some areas [1]. The challenge will be to more effectively address and remove the inequities in access to treatment and care and to implement more-effective prevention programs that reach all populations.

THE INTERNATIONAL RESPONSE TO THE EPIDEMIC

Since the UN General Assembly Special Session on AIDS in 2001, substantial increases in resources from the international community have had a dramatic impact on the landscape of the current HIV and AIDS epidemic. Specifically, increased availability of HIV/AIDS programs has been available through the Global Fund to Fight AIDS, Tuberculosis, and Malaria; the US President’s Emergency Plan for AIDS Relief (PEPFAR); and the World Bank Multi-Country AIDS Program. These initiatives have rapidly become an established part of the donor aid programs operating in countries most affected by HIV infection and AIDS. Increased funding has made antiretroviral treatment (ART) in resource-limited settings a reality, improved access to prevention services, and allowed the scale-up of evidence-based care interventions for individuals infected with HIV.

Although multiple countries have donated resources to combating the HIV pandemic, a single program, PEPFAR, was initiated in 2003 and provides funding for HIV treatment, care, and prevention both bilaterally to 15 countries and multilaterally through the Global Fund for AIDS, Tuberculosis, and Malaria. By the end of 2008, PEPFAR had provided $18.8 billion in funding for HIV/AIDS programs, and the US government had authorized up to $48 billion for continued support to help control HIV infection and AIDS, tuberculosis, and malaria. During the first 5 years, PEPFAR provided ART to 2 million HIV-infected individuals in 15 focus countries. Treatment support is estimated to have saved nearly 3.28 million adult years of life [5]. In addition to treatment, supportive care has been made available to >10 million persons affected by HIV infection and AIDS worldwide, including >4 million orphans and vulnerable children [6]. Prevention efforts have been more difficult to measure, although the goal was to prevent 7 million new infections. Dramatic increases in counseling and testing, as well as access to prophylaxis to prevent mother-to-child HIV transmission, have been documented. Antiretroviral prophylaxis was made available for nearly 1.2 million pregnant women with HIV infection, preventing perinatal HIV infection in an estimated 240,000 infants. Tuberculosis treatment was also provided to nearly 400,000 HIV-infected individuals. Despite these successes, challenges remain in treatment, prevention, and care that will ultimately need to be conquered to ensure the long-term success of these ambitious programs. Scale-up of these programs, political support, and overcoming inherent stigma and other social impediments to HIV infection must occur in the short term if these programs are to succeed.

ART PROGRAMS IN RESOURCE-LIMITED SETTINGS

More than 3 million persons are currently receiving ART in resource-limited settings as a result of the tremendous international efforts to scale up treatment during the past decade—a global health accomplishment thought to be unimaginable only 5 years ago. Treatment providers have learned many important lessons during this rapid scale-up that will be invaluable as the longevity of these critical programs is ensured. Access to care issues have posed serious challenges to national scale-up plans, with the majority of individuals in some countries not being aware of their HIV status to facilitate their entry into care [7]. Access to CD4 cell count testing to identify individuals in need of ART is critical to avoid disease progression to advanced levels in the context of which mortality during the first year of ART is far greater [8]. The pendulum has shifted toward earlier initiation of ART on the basis of excellent data showing a direct impact of ART on survival [9]. The reality in resource-limited settings is that individuals often initiate ART with CD4 cell counts of ~100 cells/mm³, in the context of which treatment is often complicated by frequent opportunistic infections and a much higher mortality [10]. National AIDS treatment plans need strategies to improve identification of persons in need of ART and to ensure timely initiation to avoid the complications of late presentation.

The public health approach to follow-up of patients receiving ART uses clinical and, if available, immunologic monitoring to identify treatment failure and to assess the need to switch to second-line regimens [11]. The limited availability of polymerase chain reaction–capable laboratories and the expense of viral load testing have resulted in only limited treatment sites having access to virologic monitoring. Several groups have illustrated the limitations of immunologic and clinical monitoring, which lacks sensitivity to identify true virologic failure and often misclassifies individuals as experiencing virologic failure when they are actually experiencing virologic suppression [12–14]. In addition, the late switching of treatment that results from this current clinical and/or immunologic monitoring has resulted in significant accumulation of genotypic resistance to ART, when individuals are identified as experiencing treatment failure either immunologically or clinically [15]. These important findings should drive the demand for robust, low-cost viral
load methodologies that could have a major impact on established ART programs.

Rural settings, transportation barriers, and the ongoing human resource crisis in most resource-limited settings have presented challenges to traditional models of treatment delivery; several innovative solutions were developed during the initial scale-up of ART. Home-based delivery of care has been a proposed solution to the issues of transportation barriers to care in rural settings, and excellent results were achieved with a home-based treatment program in Uganda [16, 17]. Task shifting of traditional health care roles has also emerged as a viable option in settings where human resource capacity is limited [18]. Few programs have evaluated the impact of task shifting, although some have shown excellent treatment outcomes in settings where task shifting has been an integral part of the care delivery model [19]. Mobile phone technology has also emerged as an important resource for health care providers to overcome communication challenges present in rural settings. Phones have been used to improve communication with central clinical services and also to provide reminders for treatment adherence [20–22].

During the past decade of HIV treatment, there has been a shift from ART in resource-limited settings being a topic of debate to a reality. The challenge now is for the international community to take the lessons learned during the initial scale-up phase to design treatment programs that deliver quality care in settings with ongoing resource constraints. Despite the tremendous achievements in scale-up over the past several years, there remains a huge unmet need in terms of the number of individuals needing ART, even with the less stringent guidelines for ART initiation used by most programs. The shift toward earlier treatment, coupled with the unfortunate reality of ongoing new infections, will challenge the already limited national HIV treatment budgets of most countries, as well as any external bilateral or multilateral support.

**HIV PREVENTION INITIATIVES**

Despite some disappointing news from the HIV vaccine research community, some tremendous strides have been made recently in HIV infection prevention. Three clinical trials showed definitively that male circumcision is an effective method of HIV infection prevention; it was associated with an ~60% reduction in the incidence of HIV infection among adolescent male individuals undergoing circumcision in these trials [23–25]. Several vaginal microbicide clinical trials are under way, offering hope that female-controlled methods of prevention could become a reality. There have been positive developments in preventing mother-to-child transmission of HIV infection from studies defining better ways to avoid ART resistance and also regimens that could prevent late transmission through breastfeeding [26–28]. Unfortunately, 2 studies examining the role of treating herpes simplex virus type 2 infection to prevent acquisition of HIV infection produced disappointing results, with no impact seen among HIV-1–uninfected individuals infected with herpes simplex virus type 2 who were treated with suppressive doses of acyclovir [29, 30]. A more recent unpublished study examining the role of suppressive acyclovir to prevent transmission of HIV infection among HIV status–discordant couples also showed that the drug does not have an impact on transmission, although some effect was seen on HIV disease progression [31, 32]. Newer biomedical prevention methods are also being evaluated, including pre-exposure prophylaxis in populations at high risk and in HIV status–discordant couples.

HIV load is the strongest determinant of HIV transmission risk [33]. Treatment for prevention has become a topic of debate as an important strategy to consider in combating the ongoing spread of HIV infection. Five studies have examined the impact of ART on transmission among HIV status–discordant couples. A meta-analysis of these studies revealed an overall risk of 0.46 per 100 person-years on the basis of 5 transmission events that occurred in these studies [34]. The ongoing study of the HIV Prevention Trials Network (HPTN 052) will provide important additional evidence regarding the usefulness of ART as a prevention method. In the meantime, the debate will continue, with recent modeling papers suggesting that early initiation of ART at the community level could have a profound public health impact on HIV transmission [35].

Program implementation and scale-up of effective prevention measures has posed a major challenge to governments and civil society organizations working to reduce the number of new infections. Despite scientific knowledge to prevent mother-to-child transmission of HIV infection through a variety of antiretroviral prophylaxis options, coverage still remains low in many areas. Some improvement has been seen in recent years, with the estimates of coverage in low- and middle-income countries increasing from 9% in 2004 to 33% in 2007. Numerous factors have challenged the scale-up of this effective intervention, including the fact that it is suited to health care delivery settings but is often implemented in areas with low antenatal care coverage, poor health care delivery systems, and culturally diverse birthing practices, often involving traditional birth attendance in a home setting. Even in settings where antenatal care is widely available, such as Bangkok, fear and stigma represent major barriers to access of effective antiretroviral prophylaxis to prevent mother-to-child transmission [36].

Despite scientific advancements in HIV transmission, political and societal barriers remain an enormous factor hampering efforts to effectively scale up HIV infection prevention programs. Stakeholders have often prioritized interventions that
are compatible with their own moral contexts and have shunned other interventions. Several at-risk populations have also been ignored in prevention efforts, with almost no services being offered to some groups (eg, men who have sex with men in Africa) who engage in ongoing risky behavior and are often a bridge population to other groups in the general population [37]. The scientific community has learned that prevention of HIV infection is extremely complex, and translation of scientific findings into measurable results will be possible only through comprehensive strategies. The challenge will be to convince leadership groups to adopt comprehensive prevention strategies that offer a broad range of methodologies catering to diverse and often underserved populations.

EMPHASIS ON BUILDING IMPROVED HEALTH CARE DELIVERY PROGRAMS

Simple interventions, such as access to safe water and maternal health services, often have a profound impact on public health. Several basic interventions have been shown to greatly improve the health of HIV-infected persons in resource-limited settings and have a direct impact on disease progression, morbidity, and mortality. Trimethoprim-sulfamethoxazole prophylaxis was shown early in the HIV epidemic to work as an effective prophylactic agent against Pneumocystis jirovecci pneumonia in patients with CD4 cell counts <200 cells/mm³. In Africa, trimethoprim-sulfamethoxazole was shown to reduce morbidity and mortality among HIV-infected individuals, who also experienced fewer malarial episodes and hospitalizations [38]. Provision of a safe water vessel (eg, basic plastic water container with bleach added for purification) has been shown to dramatically reduce the number of episodes of diarrheal illness among HIV-infected individuals [39]. The provision of a basic care package was adopted early after initiation of the PEPFAR program, with the goal of improving outcomes of HIV infection, even in the absence of ART.

One myth that needs to be dispelled in the current state of HIV/AIDS programs in resource-limited settings is that investments in these programs have been at the expense of other global health programs and also at the detriment of the current fragile health systems in the host countries. On the contrary, the current HIV/AIDS initiatives have exposed serious weaknesses in the existing health infrastructure in many countries and have also made valuable contributions to rebuilding broken health systems through a variety of mechanisms. For example, 35% of spending of the Global Fund to Fight AIDS, Tuberculosis, and Malaria contributes directly to supporting human resources, infrastructure, and equipment and systems for monitoring and evaluating programs. All of these components are fundamental pieces in the development of health systems. PEPFAR has also committed significant resources (~$4 billion during the first 5 years) to building health systems in the countries where HIV/AIDS PEPFAR programs are being implemented. HIV/AIDS treatment programs have also been shown to reduce admissions to health care facilities by up to 21%, ultimately reducing the strain on these resources and allowing health care workers to focus on other health care needs [40]. Now that the emergency phase of ART scale-up appears to be moving toward creating sustainable, quality programs delivering care, international partners should continue to focus on innovative ways to build health systems to improve the health of populations in the future.

In the reauthorized PEPFAR legislation from 30 July 2008, an additional $48 million was authorized over the next 5 years to combat global HIV infection and AIDS, tuberculosis, and malaria. Additional targets were set to provide treatment for at least 3 million infected persons, to prevent 12 million new infections, and to provide care for 12 million persons, including 5 million orphans and vulnerable children. In addition, this renewed initiative added several other targets that were aimed at helping to address health infrastructure and capacity building in general in the focus countries and elsewhere. For example, to meet the aforementioned goals and to build sustainable local capacity, the new legislation called for training at least 140,000 new health care workers in HIV infection and AIDS prevention, treatment, and care. Five billion dollars was allocated for improved malaria control programs, and $4 billion was targeted solely for programs to fight tuberculosis. The legislation specifically called for an increase in microbiode research and other biomedical interventions to help prevent HIV transmission. Finally, the legislation allowed for the construction of medical facilities in a foreign country to assist in the care of individuals and included a direct statement to strengthen the capacity of developing countries to purchase and provide vaccines for related infectious diseases and to provide improved nutritional support and other essential medical care for individuals affected by these infections. Additional funding could also be made available in proposed legislation to improve maternal and child survival from a variety of causes, thus broadening the mandate of global health through these activities. The challenge for the future will involve how to incorporate and integrate many of these well-intentioned activities, some of which are targeted at a few diseases, to sustain an improved primary health care system that can achieve the health goals of the country.

CONCLUSIONS

The achievements of the past 6 years in HIV infection and AIDS treatment, prevention, and care are astounding in retrospect. PEPFAR has been the most ambitious initiative to address the global HIV epidemic, providing the majority of its budget to 15 focus countries, 12 of which are in Africa. In a recent analysis of the 12 African PEPFAR focus countries, treatment and care programs appear to have reduced the number
of HIV infection–related deaths by 10.5%, or ~1.2 million deaths were averted because of PEPFAR’s activities [5]. As PEPFAR; the Global Fund to Fight AIDS, Tuberculosis, and Malaria; and other HIV/AIDS programs continue their efforts, it will be of critical importance that researchers and persons implementing programs work together to develop the best metrics to measure impact of these programs over time. Detailed program evaluation and accountability of the original goals of the current global HIV/AIDS initiatives are an absolute necessity to justify the ongoing and expanded efforts to mitigate the effects of HIV infection and AIDS. Continued strengthening of global monitoring and evaluation systems will be crucial to improve decision making and to ensure effective delivery of services. Prevention and treatment services need to evolve as a comprehensive package designed to suit the local needs of societies and not the ideals of politicians and special interest groups. Finally, only through continued political leadership that embraces human rights and discourages social stigmas at all levels, regardless of race, sex, or sexual orientation, will the global health community be able to win the ongoing fight against the spread of HIV infection and AIDS.

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