Global Antiretroviral Therapy: The Hope Within Pandora’s Box?

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ABSTRACT

The vast numbers of individuals now infected with the HIV-1 virus and its spread to all corners of the globe have been well chronicled. It is difficult to convey, however, the desperation and hopelessness of the majority of those HIV-1-infected individuals that live in regions where resources are sparse. Pursuit of the unique and complex medical and societal issues relating to the HIV pandemic is globally creating a discrete area within the field of infectious disease. The consequences of the severe immunologic compromise resulting from HIV-1 infection vary from those seen in the West, both in terms of entities and their frequency. While a number of antiretroviral distribution programs are in place, the development of guidelines that simplify antiretroviral regimens, enrollment in treatment programs, and monitoring remain difficult. Furthermore, the epidemiology, response to antiretroviral therapy, and resistance patterns of non-B subtypes await further elucidation. The goals that have been set may be compromised by concomitant endemic diseases (such as tuberculosis and malaria), unpreventable mother-to-child transmission, malnutrition, poor sanitation, inadequate public health systems, and, especially, the lack of an adequate healthcare workforce. However, awareness of these impediments is growing. The understanding of the complex and diverse economic, political and cultural forces entwined with and driving the epidemic is evolving. Finally, the need for a long-term, multifaceted response to the broad crisis in underdeveloped nations where AIDS is but one of a number of critical elements is becoming appreciated.

GLOBAL HIV-1 MEDICINE IS A DISTINCT ENTITY

We adoringly call them the “Shashemene Kids.” Barely 20 years old and with no medical training whatsoever, they have assumed responsibility with extraordinary courage and humility. The town of Shashemene is about four hours drive south of Addis Abeba, amongst the Rift Valley Lakes. A crossroads for southern Ethiopia, it sprawls over a large area. It is crowded and poor, its myriad unpaved passageways stringing together meager earthen dwellings interspersed with brightly colored fruit and vegetable markets. AIDS abounds in Shashemene, where seroprevalence was estimated at 13% in 2002 (United Nations Children’s Fund/WHO/UNAIDS, 2004). Advanced AIDS patients are often cast away here, once their emaciation and debilitation make the diagnosis impossible to camouflage.

Appalled by the situation and undaunted by either their lack of training or any support, the “Sheshamene Kids” began to provide solace and care. Inside a small dirt compound, encircled by a few dark rooms furnished with only the most thin and tattered of mattresses, they gave a home to the abandoned, impoverished, and desperately sick. With kindness and vigilance they attend to their patients’ every need to the best of their abilities and resources. They rejoice in what is possible, and are undeterred by what is not.

We finally found them on a Sunday morning. The three of us were all clinicians well experienced with the toll the HIV-1 virus can take on the human body. Our hosts were excited that we had come and were honored that we wanted to see their patients. Of their approximately 20 charges, the ones who could still walk had gone to church with some of the staff. We saw those who could not go. One lady was febrile and diaphoretic, had a massively enlarged and tender spleen, and could not sit up. Another young woman was febrile, tachypneic, and coughing incessantly. A third lady was barely arousable, almost immobile, and wasted to a mere skeleton. A fourth lady was in agony with shaking chills and an acute abdomen. There were others. There was no medical care and no medicine. Once infected with HIV-1, the inexorable progression to suffering, debility, humiliation, and early death is the reality for most individuals in poor countries. Each individual death often leaves an additional wake of misery in the form of infected sexual partners, infected children, the inability of the family unit to sustain itself, and orphans. Since 1999, the average life span for persons born between 1995-2000 has now decreased by...
13 years to 49 years in seven African countries with HIV seroprevalences exceeding 20% (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2004a). In Swaziland, Zambia, and Zimbabwe the life expectancy of those born in the next decade may drop below 35 years without antiretroviral therapy (ART) (UNAIDS, 2004a).

The medical and social science of the global AIDS pandemic is rapidly becoming a distinct arena within the field of HIV medicine. The opportunistic consequences of HIV-1 infection vary both in terms of entities and the magnitude of disease burden. The HIV-1 epidemic confounds and is confounded by existing concomitant epidemics of tuberculosis, malaria, and other sexually transmitted diseases. HIV is the most powerful known risk factor for reactivation of latent tuberculosis infection. Once infected with tuberculosis, there is an increased risk to develop active tuberculosis with increased likelihood of disseminated disease. There is also increased risk of re-infection with tuberculosis for those infected with HIV-1. To succeed in managing tuberculosis, HIV must be addressed; to address HIV, tuberculosis must be controlled.

Tuberculosis competes with bacteremias as the most common of HIV-related infections (Holmes et al., 2003). Prominent bacteremias include those from non-typhoidal Salmonella species and Streptococcus pneumoniae. Diarrheal diseases are prevalent, caused not only by bacterial pathogens, but also by the entities of cryptosporidiosis, microsporidiosis, and isosporiosis (Holmes et al., 2003). Fulminant neurological disease is common, especially as a result of toxoplasmosis and cryptococcal meningitis. For the majority of these infections, diagnostic tests and many therapeutic modalities, both for treatment and prophylaxis, are either unavailable or are only sporadically available. Furthermore, it is now accepted that there are significant interactions between malaria and HIV, especially in pregnant women (Ter Kuile et al., 2004). Co-infected
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Pregnant women experience more frequent malaria (both peripheral and placental), a higher level of parasitemia, and more severe anemia. Their infants also have lower birth weights (Ter Kuile et al, 2004).

Mother-to-child transmission (MTCT) of HIV-1, virtually eliminated from developed countries, continues almost unabated in the less privileged regions of the world, where ART is not available, where the reproductive health care infrastructure is minimal, and where alternatives to breast-feeding are usually not affordable, sustainable, safe, or culturally acceptable (World Health Organization (WHO), 2004a). The toll is staggering, especially in sub-Saharan Africa, where more than 500,000 infants were vertically infected in 2003. Without intervention, 25 to 45% of HIV-1-infected women who breastfeed will transmit HIV-1 to their infants; almost double the 15 to 30% transmission rates that occur cumulatively through pregnancy and during the peripartum period (WHO, 2004a). Following publication of the initial vanguard study of the three-part prophylactic regimen of AZT in the US (Conner et al., 1994), further clinical trials and observational studies have proven the effectiveness of shorter, simpler, and less expensive MTCT regimens in resource-limited settings (WHO, 2004a). Further trials are underway or planned to evaluate infant prophylaxis for varying periods of time postpartum, or to provide maternal ART during breastfeeding for women who otherwise would not meet ART initiation criteria (Newell and Thorne, 2004). Drug resistance in mothers and infants induced by regimens to prevent MTCT that do not fully suppress the virus is a growing concern. The clinical consequences of viral resistance following short-course prophylaxis to prevent MTCT and the potential to compromise future ART are pressing issues under investigation.

Beyond the prevention of MTCT, the international community has now launched a massive effort to expand access to ART globally (WHO, 2003a). It is committed to find ways to translate the HIV-1-related care and ART that evolved in the context of the tertiary care available in the US, Europe, and Australia for application in areas of the world in which almost no infrastructure exists. These are areas in which HIV-1 subtype B, found most commonly in the West, does not predominate. There is much to be clarified and described in terms of the transmission efficiency, pathogenicity, efficacy of antiretroviral drugs, and patterns of drug resistance for the multiple other HIV-1 subtypes that are prevalent in these areas. The World Health Organization (WHO) has crafted guidelines for staging HIV-1 disease and initiating ART in resource-constrained settings, has recommended first- and second-line treatment regimens, and has suggested tiers of laboratory tests for enrollment and monitoring based on availability (WHO, 2003a).
THE HIV-1 CRISIS ON AN INDIVIDUAL LEVEL

It is one thing to know that minimal infrastructure exists; it is an entirely different matter to try to function in such settings. Consider the following situation of one young woman being evaluated for a demonstration project to provide ART in Addis late in 2004. Although she did not know her birthday, by her family's historical account she was about 36 years old. Both her husband (who had been in the military) and she were health assistants and had worked in hospitals. She had been married to her husband, her only sexual partner, for about 10 years. He had died five years prior following a wasting illness that she presumed was AIDS. She had been unwell since her husband's death and was treated for nine months until the spring of 2004 for inguinal TB lymphadenitis. At the completion of the tuberculosis treatment she had weighed about 110 pounds. During the intervening eight months she had become much weaker with anorexia, dysphagia, and fever; she was unable to work and provide food for her two children aged six and ten. She was admitted to the hospital in late 2004, delirious, with a temperature of 104°F, weighing about 90 pounds, and with severe oral and presumed esophageal candidiasis. The only laboratory examination was a hemoglobin level of 7.5, a white blood cell count of 3,250, and a blood smear, which demonstrated no hemoparasites. On a treatment regimen of ceftriaxone and gentamycin her temperature began to abate from 102-104°F to 99-100°F over the ensuing several days. Her mental status improved although she was too weak to get out of bed, but she then experienced two grand mal seizures. With no ability to measure electrolytes, determine acid/base status, image her brain, or evaluate her otherwise for AIDS-related CNS pathology, she was simply monitored. Although we could not further define co-morbidities and HIV-1-related co-infections, we planned to start her on ART. Unfortunately, she died within the next two weeks, before that could be done.

AIDS IN THE CONTEXT OF A BROAD CRISIS IN UNDERDEVELOPMENT

The failure of developing countries to better cope with the AIDS pandemic, especially countries in sub-Saharan Africa, is symptomatic of a poor economic state and thus, fundamental inadequacies in their healthcare delivery systems. Ethiopia, for example, is one of the poorest countries worldwide, with a per capita annual income only reaching US $100 (UNAIDS, 2004b). Crippled by limited resources (even where foreign assistance flows freely), the ability of developing nations to combat AIDS as well as a host of other endemic diseases, such as tuberculosis and malaria, is compromised by weak infrastructure, concomitant issues such as malnutrition and poor sanitation, and inadequate public health systems (see Figure 1).

The WHO-supported Commission on Macroeconomics and Health estimated that healthcare spending in the poorest countries of the world is approximately US $57 billion short of the minimum required for the provision of non-AIDS-related basic care (Commission on Macroeconomics and Health, 2001). Although there are a number of contributory factors behind the continuing collapse of healthcare infrastructure, chief among them is reduced public expenditure on health. For example, 26 of the poorest African countries fall below the US $60 per capita figure advocated by WHO-affiliated health economists (Evans et al., 2001). Yet, despite continuing civil society advocacy and for myriad reasons—none of which is acceptable—public health spending in developing countries, both per capita and as a percentage of gross domestic product (GDP), remains considerably lower than in economically sound G8 nations (United Nations Development Programme, 2004).

Health systems in the developing world would still be overburdened even without AIDS. For example, other infectious and parasitic diseases killed roughly 3.5 million people in Africa in 2002 (WHO, 2004b)—more than half as many as died from AIDS that same year (WHO, 2004b; UNAIDS/WHO, 2002). Tragically, AIDS is very much present, and it is in full assault against developing countries, straining their already strained health systems. So much so that despite an influx of resources directed against HIV/AIDS (as well as other endemic diseases of poverty), the absence of an effective public healthcare system in poorer countries undermines interventions supported by donors such as the Global Fund Against AIDS, Tuberculosis & Malaria (Global Fund). Indeed, the Global Fund's initial assessment of the situation in AIDS-ravaged Africa predicted that “the greatest burden of [AIDS, tuberculosis, and malaria] falls on Africa... [where] AIDS, and [tuberculosis] linked to AIDS, and malaria, are straining an already frayed public health infrastructure (United Nations Children Fund/UNAIDS/WHO, 2000).”

Personnel Shortages

Perhaps the most serious reflection of the collapse of health systems—and one of the greatest threats to expanded access to antiretroviral therapy—lies in the situation regarding health personnel. While data lag far behind their need for quantitative and qualitative purposes and, indeed, prove difficult to compile, a number of institutions have, through various mechanisms, identified significant weaknesses in human resource availability and capacity. Among these are shortages of personnel to deliver care, insufficient training to allow for the delivery of optimal care, lack of support to facilitate its delivery, and the absence of incentives through which health personnel may remain on the front-lines of care delivery (Narasimhan et al., 2004; World Bank, 2003). Some health systems analysts
have suggested that current efforts to scale-up access to ART may fail as a direct result of these weaknesses (Kober and Damme, 2004).

With regard to personnel shortages, physician to patient ratios in most developing countries fall well short of expectations—and have done so as a matter of historical perspective. According to a US Agency for International Development (USAID) study, in countries such as Ethiopia and Tanzania, the physician to patient ratio stands at 1:≥30,000; the situation is not much improved in countries such as Côte d’Ivoire and Senegal (1:10,000); and, while certainly more reassuring, the physician to patient ratio in more affluent countries such as Botswana and South Africa (1:5,000) remains an obstacle to the provision of quality care (USAID, 2003). The human resources crisis similarly affects other health professionals—including nurses, most of whom bear the brunt of care in the developing world. Nurse to patient ratios range from 1:≥10,000 in Mali, to 1:5,000 in Uganda (USAID, 2003). While no one argues that this ratio should mirror that of developed countries (average = 1:300 physician to patient; 1:1,000 nurse to patient [USAID, 2003]), there must be a concerted effort to address this burgeoning crisis.

**Insufficient Training**

Insufficient appropriate and/or adequate training—without which any hopes for the safe and optimal delivery of antiretroviral therapy may be dashed—exacerbates the burden created by personnel shortages. An American Foundation for AIDS Research (amfAR) study revealed, for example, how a severe shortage of trained physicians in Asia may be slowing progress in scale-up efforts. According to the study, among six high-burden Asian countries, the HIV-trained physician to HIV-positive patient ratio varies from a high of 1:3,140 in Cambodia to a low of 1:11,250 in Vietnam (amfAR, 2004).

Yet, even among those physicians considered “trained” via various educational interventions, there exist such overwhelming knowledge gaps that the need for an increased focus on human capacity-building is crystal clear. Field-testing by the International Association of Physicians in AIDS Care (IAPAC) of a proctored certification examination among a group of developing world physicians identified major gaps in knowledge deemed necessary for the management of antiretroviral therapy in resource-limited settings. Among 250 African physicians taking the examination, whose passing score is 70 percent or higher, the average scores across four critical areas of ART delivery were: 46.85% (delivery of adult/adolescent antiretroviral therapy), 40.80% (pediatric antiretroviral therapy), 61.02% (prevention of mother-to-child transmission), and 38.46% (occupational post-exposure prophylaxis) (IAPAC, 2004a). These gaps, if not addressed, jeopardize not just the short-term goal of placing more patients on ART, (WHO, 2003b) but the longer-term aim of keeping patients on ART, achieving viral suppression, and mitigating the onset of antiretroviral drug resistance.

**Lack of Clinical/Technical Support**

In those countries in which antiretroviral therapy programs have been launched—in however limited a manner—there also exists a general misconception that one-time (or silo) training activities of varying intensity represent sufficient capacity-building interventions. Given the lack of formal HIV/AIDS-specific pre-service training provided in most developing world medical schools, and the relative ad hoc nature of vertical training activities coordinated by disparate (albeit like-minded) academic institutions, as well as non-governmental and non-academically-affiliated entities, there is a pressing need for ongoing clinical support of physicians and allied healthcare professionals via various means. These include, for example, technology-facilitated warmlines and continuing education (CE) activities, as well as technical assistance around program implementation. However such support is neither in abundance nor is it consistently implemented. For example, only a handful of more affluent developing countries are experimenting with technology-based mentoring; and too few have regulated CE activities as a means to guarantee continuous educational/practical reinforcement for health-care personnel (IAPAC, 2004b). As for technical assistance targeted at successful program implementation, this remained in scarce supply until very recently, when numerous institutions such as the WHO, Clinton HIV/AIDS Initiative, and USAID ramped up their respective efforts in this area (Institute of Medicine, 2004).

**Lack of Resources**

Sadly, even where health personnel are trained and offered support, there remains a lack of incentive to secure their involvement in the clinical management of HIV/AIDS either beyond a few years or within their countries. In addition to the stigma that continues to be associated with HIV disease—among patients, families, care providers, and communities—there is the reality that AIDS does not exist in a vacuum. Co-existing with endemic diseases such as tuberculosis and malaria, and illnesses caused by malnutrition and poor sanitation, HIV disease places strains not just on health systems, but also on health professionals.

A recent study in support of the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) illustrated the burden by reflecting on per-patient time requirements in minutes across a cadre of health personnel managing a patient on ART, assuming no delegation of duties to community health workers. Assuming scale-
up of access to ART for 10,000 patients in Zambia, the study calculated 90 minutes per year of a physician's time required per patient just for the management of ART; not to mention an additional 105 minutes per episode per patient to manage complications such as oral candidiasis and meningitis, as well as co-infectious diseases such as tuberculosis (Smith et al., 2004). Under this scenario—understanding that time requirements will vary based on whether a patient is being initiated versus maintained on ART the researchers estimated a need for 206 physicians by 2006 dedicated to deliver such care; a figure that represents close to one-third of Zambia’s existing physician workforce (Smith et al., 2004). When one-third of a country’s physicians are required to deliver quality ART-based care, the challenge of delivering other priority and non-priority health services becomes glaringly evident.

Another challenge lies in the fact that a significant percentage of physicians and allied health professionals from the developing world are lured to more developed or outright developed countries by the incentive of higher wages, improved living conditions, and increased opportunity for career advancement (Padarath et al., 2003). Additionally contributing significantly to this “brain drain” is the frustration and disillusionment experienced when professionals are unable to apply medical knowledge to improve individual lives due to lack of diagnostic and therapeutic modalities and support staff. Another recent study of the health personnel workforce in Zambia found that the average loss of HIV/AIDS service delivery staff was 30% annually, predictably complicating the expansion of ART program (Huddart et al., 2004). “Brain drain”, however, occurs not only as professionals leave their countries, but also as they distribute themselves within countries. They gravitate to the private sector from the public sector where income is more lucrative, resources are more available, and there is greater autonomy; they gravitate to the urban from the rural settings.

Certainly, the crisis around health personnel is but one in a mix of other interrelated factors such as crumbling (or non-existent) physical infrastructure and inefficient (or unreliable) drug supply chains. Nonetheless, this crisis poses perhaps the greatest risk because without the health professions to educate, administer care, and monitor its progress, the miracle of modern medicine espoused by ART (and taken for granted in developed countries where such health personnel crises are rare) could escape countless men, women, and children living with HIV/AIDS in the developing world.

LOOKING TOWARDS THE FUTURE

When mythical Pandora opened the forbidden box, it spewed forth a horde of miseries into the world. The only good that it contained, intact at the bottom of the box, was hope. To this day it remains man’s comfort and salvation. An internationally galvanized response to the world’s crisis in underdevelopment, especially in Africa, with a pragmatic and strategic long-term response to the AIDS pandemic as its centerpiece, is a hope that can be realized. This hope has recently been inspiring portrayed in two documents.

The National Academy of Sciences insightfully summarizes the current situation, and especially highlights the dearth of healthcare workers that existed in much of the less-developed world even before the current pandemic occurred (National Academy of Sciences, 2005). It boldly proposes the creation of a U.S. Global Health Service as a new national program to provide US expertise to help host countries establish and sustain their health workforce and capacity. The proposal provides plans for six linked areas under a single management structure including designs for (1) a global health service core, (2) a health workforce needs assessment capability, (3) a fellowship program, (4) a loan repayment program, (5) a twinning program and (6) a clearing house for information collation and exchange. Finally, it considers ways to sustain developing health forces by addressing the needs for long-term health force capacity development, creative partnerships, electronic technology and global health education within the U.S.

The second document is a richly textured book published by UNAIDS and entitled “AIDS in Africa—Three Scenarios to 2025” (UNAIDS, 2005). It projects into the next two decades and analyzes three different pathways the global community can adopt to confront the AIDS epidemic. The first scenario entitled “Traps and Legacies: The Whirlpool” extends the current trends for the next twenty years. It illustrates that

“...it will be difficult to make a difference in the AIDS epidemic if HIV is viewed in isolation from its root social, economic, and political context; or if it is seen only as a medical problem or as an issue of individual behavior change...”

In this scenario, the continent is gripped in a downward spiral of disunity, denial and stigma, contested knowledge, wasted resources, and competing sources of power and authority. The capacity of systems, people, and institutions to respond to the crises of AIDS and underdevelopment are systematically diminished.

The second scenario, entitled “Tough choices: Africa takes a Stand”, describes what might transpire if African countries, especially if collectively, mobilize and nurture their own resources. In this setting, international aid falters after an initial spurt of interest. This scenario demonstrates that
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"while there are enormous odds to overcome, there is much that countries in Africa can do with their own strength to grow their economies, to prioritize developmental objectives, to lay the foundation for future growth and development, and to reduce the incidence and prevalence of AIDS."

In this scenario, effective African leadership at the national and community levels make the choices needed to accrue long-term benefits for their own cultural, economic, and human potential.

In the third scenario entitled “Times of Transition: Africa Overcomes,” African governments stress “Pan-African solidarity and high levels of regional co-operation…and put public good before private office,” much as in the second scenario. In this last scenario, however, the AIDS pandemic additionally acts as an international catalyst fostering “a new global covenant, involving security and human rights agendas brought together in a coherent international framework that encompasses economics, trade, social justice, and political reform.” In such an environment, national autonomy is promoted, African resources are consistently amplified in ways that do not engender dependency, and marked strides in health care development are possible.

CONCLUSION

As we move forward early in this twenty-first century we must harness the lessons learned during the first 25 years of the human experience with HIV. This knowledge must color the decisions made now if we are to halt the complex forces driving the AIDS pandemic. The outcome is not at all determined at the present time, but the actions we take today will shape the evolution of the AIDS pandemic far into the future. We are provided choices at all levels. It is essential that we embrace those with a lengthened perspective that will ensure the development of effective policy and systems with capacity and resources.

REFERENCES


