Scaling up access to HIV prevention, treatment, and care in resource-poor settings: challenges and opportunities

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Abstract

Communicable diseases remain the major cause of morbidity and mortality in resource-poor settings. Through both biological and social mechanisms, poverty greatly enhances the vulnerability of people to many infectious diseases. Vice versa, the major infectious scourges like HIV/AIDS, tuberculosis and malaria, perpetuate poverty and are an important contributor to negative economic and social development. HIV/AIDS is a case in point, because it primarily affects people in the prime of their lives, leading to losses in productivity and social cohesion. Its effects are most dramatic in sub-Saharan Africa, where the situation is often aggravated by the fact that so many countries are suffering from weak or dysfunctional governance. The latter has contributed to a steadily progressive erosion of the public health sector in those countries. HIV/AIDS also fuels a tuberculosis epidemic. On one hand we are dealing with greatly increasing demands on the public health sector, especially in countries hardest hit by the HIV/AIDS epidemic, on the other hand that health sector is losing already scarce workers to HIV/AIDS. Likewise, the capacity of the education sector is weakened because of increased mortality of HIV-infected people teachers.
In an era of globalization, the world cannot afford to ignore the health (and other) problems of developing countries. Humanitarian motives aside - which alone should be enough reason for action - the downward spiral of economic and social development in the poorest countries presents a recipe for global insecurity and instability. Despite the progress that has been made during the past few years in the closing of the “funding gap”, implementation of effective interventions in countries has been lagging behind.

There is great need for global leadership in the fight against HIV/AIDS and for a global action plan, that takes a pragmatic approach, based upon the best of science and empirical evidence. The challenge is formidable, but the current momentum for the antiretroviral scale-up provides a unique opportunity to empower the poor and build sustainable health care systems in Africa and other resource-poor settings.

Introduction

The human immunodeficiency virus (HIV), the causative agent of the acquired immune deficiency syndrome (AIDS), creates havoc in many developing countries. Approximately 40 million people are now living with this virus, of
which over 25 million live in sub-Saharan Africa, and over 7 million in South and South-East Asia [Figure 1]. Since the emergence of the epidemic in 1981, approximately 20 million people have died from HIV/AIDS and it has become the leading cause of death of individuals aged 15-49 years in many of the countries concerned. In the hardest hit countries, such as Botswana and Swaziland, HIV prevalence rates in this age group approach 40%. In 2004, almost 5 million people became newly infected with HIV and over 3 million people died from HIV/AIDS. There is a rapidly growing epidemic in Eastern Europe and Central Asia, which was initially driven by intravenous drug users but is now spreading to other segments of the population [UNAIDS 2004].

The HIV/AIDS epidemic is a humanitarian disaster on an unprecedented scale. But due to the “target population” of this disease and its invariably lethal nature if left untreated, it is much more than that. To quote Epstein: “The mortality and morbidity associated with AIDS make it unlike most other types of sickness and disease. Whereas most diseases prey largely on the very young, the old, or the weak, the way in which HIV is contracted and spread makes young adults and especially young women, the most vulnerable. As a result, in countries with high HIV prevalence, the socioeconomic consequences of high mortality among adults can be far-reaching, devastating households, families, and communities and eroding formal and informal mechanisms of social support.” [Epstein 2004]. HIV/AIDS is a health emergency, but it is also a broad long-term development issue. Moreover, it is an important driver of the global tuberculosis (TB) epidemic [The Stop TB Partnership 2004].
Apart from briefly discussing some of the above-mentioned consequences of HIV/AIDS, this paper takes stock of interventions that could stem the epidemic and mitigate its impact, and of some of the obstacles that have to be overcome to achieve this.

Social and Economic Consequences of HIV/AIDS

HIV/AIDS is having a profound demographic impact, reversing gains in life expectancy and improvements in child mortality in many countries [Epstein 2004]. Mortality among the population aged 15-49 has increased manifold, even in countries with modest epidemics. In the absence of broad access to treatment, HIV/AIDS will result in radical changes in the structure of the population of hardest hit countries, with a striking gap in the productive and caregiver part of the population, leaving the young and old to cope alone, and reversing economic and social development.

There is an increasing feminization of the epidemic, especially in sub-Saharan Africa, with young women being particularly vulnerable to acquiring HIV, for biological, cultural, social and economic reasons. In sub-Saharan Africa, the peak HIV prevalence occurs at a younger age and at a higher rate among women than among men [UNAIDS 2004]. Infant and child mortality rates go up, because of HIV transmission from HIV-positive mothers during pregnancy, delivery and breastfeeding, but also because mothers and fathers and other adults that could care for them die. There are currently more than 15 million AIDS orphans; in some countries three quarters of all orphans are AIDS orphans, stretching the limits of extended families, and contributing to the vicious cycle of inadequate education, poverty and disease.

At the household level income declines as breadwinners fall ill and die, and as other household members are obliged to take time off from other productive activities to care for sick relatives.
Simultaneously, households have to devote an increasing share of their income to health care and funerals.

The sector most directly affected by HIV/AIDS is the health sector. On one hand, demands have risen sharply because of HIV/AIDS, on the other hand, already scarce health personnel is affected by the disease as well. Likewise, the capacity of the education sector is weakened because of increased mortality of teachers.

The impact of HIV/AIDS goes far beyond disruption of more or less tangible economic or administrative processes within households, businesses, or government agencies. It may disrupt the very fabric of society, leading to political instability and deteriorating security at the individual, community and national level [Haacker 2004].

HIV/AIDS and tuberculosis

Dual HIV/TB infections form an exceptional challenge. Worldwide 14 million people are co-infected with these pathogens and TB is a leading cause of death among people living with HIV [The Stop TB Partnership, 2004]. HIV infection increases the risk of reactivating latent \textit{M. tuberculosis} infection, placing HIV-positive persons at increased risk for developing TB [Bucher and others, 1999]. HIV infection also increases the risk of rapid TB progression after primary \textit{M. tuberculosis} acquisition or reinfection [Daley and others 1992]. TB may accelerate the progression of HIV disease via immune activation and is associated with a higher mortality and shorter survival in HIV-positive persons [Whalen and others 2000]. The risk of TB increases as the HIV-related immune deficiency progresses; similarly, the highest mortality rates associated with TB
occur in persons with the greatest immune deficiency [Shafer and others 1996]. However, there already is a rapid increase in TB incidence soon after infection with HIV [Srikantiah and others 2005, Sonnenberg and others 2005]. The presentation of TB in those with advanced HIV disease is often atypical, and a documented bacteriological diagnosis may be more difficult to make [Jones and others 1993]. Concomitant treatment of HIV and TB also poses difficulties. In those with dual infections who initiate anti-HIV therapy (antiretroviral treatment) in advanced stages of HIV infection there is a high rate of immune reconstitution disease, leading to considerable early morbidity and mortality [French 2004]. There are overlapping drug toxicities [Lee 2003] and pharmacological interactions between anti-TB drugs and antiretroviral agents, considerably narrow antiretroviral treatment choices in those who need concomitant treatment. It is no exaggeration to state that successful global control of TB very much depends on our ability to prevent and treat HIV infections.

Prevention of HIV infections: where do we stand?

Despite successes in curbing the HIV/AIDS epidemic in individual countries, global figures continue to grow. More people became infected with HIV in 2005 than in any year before [UNAIDS]. What drives the epidemic differs between and within regions and countries, but a common denominator is that it strikes disproportionately at vulnerable and marginalized groups in the societies concerned: youth, women, sex workers, migrant workers, injecting drug users, homosexual men; those unable to protect themselves adequately against
infection for a variety of social and biological reasons [UNAIDS]. HIV is a virus, but inequity is at the roots of most of its spread. Condoms are highly effective at preventing sexual transmission of HIV, but only if they are available and used [Weller 1993]. Even if the former is the case, women are often in a difficult position to negotiate use by their male partners [Allan ..]. Needle exchange programmes and substitution therapy for injecting drug users are effective at lowering HIV transmission rates within this population, but are often politically unacceptable in the very countries where the epidemic is fueled by intravenous drug use [UNAIDS].

It is clear that the world has to fight the current “prevention fatigue”, and step up HIV/AIDS prevention efforts in a comprehensive and non-dogmatic manner, but at the same time we should recognize that only an effective preventive vaccine can deliver a future without HIV/AIDS. Unfortunately, despite initial optimism, evolving scientific insights tell us that there is still a long way to go here. The major challenge is to develop immunogens that are capable of neutralizing primary HIV isolates from all genetic subtypes and regions of the world. The good news is that after many years of misguided and haphazard efforts, the global scientific community is now committed to a coordinated, collaborative and systematic process to develop the vaccine [Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise 2005]. Given the formidable scientific challenges that the design of an effective HIV vaccine poses, it is hard to predict if and when such a vaccine will be available, however. There is thus an urgent need to develop alternative prevention technologies, especially those that would be “female-controlled” (i.e. use of which would not require the consent of the
male partner). Thus the thrust to develop vaginal microbicides [Shattuck and Moore 2003]. Unfortunately, first generation microbicides, all based on aspecific spermicides such as nonoxynol-9, in studies in high-risk populations led to more HIV-1 transmission at worst [Kreiss 199..], or were not effective at best [Van Damme 2002]. The newest generation of vaginal microbicides under investigation utilizes classes of HIV-specific inhibitors that are also used in or developed for therapeutic purposes [Di Fabio and others 2003, Lederman and others 2004], but the clinical development is still at a very early stage. Likewise, oral antiretroviral pre-exposure prophylaxis (PREP) may also be effective in preventing sexual transmission of HIV [TDF....]. This approach is currently being investigated in several high risk populations across the globe, although recent animal studies seem to point at limitations of the specific drug utilized [Subbarao 2005].

The use of antiretrovirals for the prevention of mother-to-child transmission, introduced in 1994, has been highly successful. Unfortunately, as with the antiretroviral scale up (vide infra), cost and logistical considerations dictate widespread use of a suboptimal drug regimen in most developing countries, which, apart from limited efficacy, may also negatively affect future treatment outcomes for mothers [Jourdain 2004] and contribute to an increase in circulation and transmission of drug-resistant viruses [Jackson 2001]. Another issue that was initially downplayed in the exaltation about the success of short-course peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV-1, is subsequent transmission via breastfeeding in populations where this practice is the norm and where formula feeding is not an alternative [Petra Study...
Group 2003]. Infant-PREP during the period of breastfeeding may minimize this risk [Vyankadondera 2003].

Treatment of HIV infections where do we stand?

The success of highly active antiretroviral therapy (HAART) is an illustration of the fact that in medicine quantitative insights can make a dramatic qualitative difference. Effective antiretroviral agents have been available since 1987 [Fischl 1987]. First generation antiretrovirals are still components of many antiretroviral drug regimens that are used today. The antiviral efficacy of HAART indeed is not only due to the appearance of drugs with new mechanisms of action, but primarily to using combinations of at least three anti-HIV drugs that inhibit viral replication to such an extent that development of viral drug resistance is smothered (provided the drugs have non-overlapping resistance patterns) [Lange 1997]. The ability to measure the amount of virus in blood and other body compartments, through molecular amplification techniques that became available in the mid-1990’s, has been of crucial importance in the realization that prior approaches of using one or two drugs could not suppress viral replication in a durable manner.

The introduction of HAART is one of the great success stories of modern medicine. Its impact on HIV-related morbidity and mortality can almost be compared to that of the introduction of penicillin on pneumococcal pneumonia half a century earlier. Those of us who have witnessed this turning point in the availability of therapeutic perspectives for people with HIV/AIDS cannot think
about it without an immense feeling of satisfaction and gratitude. However, in contrast to pneumococcal infections, HIV infections are chronic and therapy is not curative. This implies that antiretroviral therapy, unlike a penicillin course, is a longlasting (lifelong) affair. This poses formidable challenges.

First of all there is the problem of patient adherence: taking drugs according to prescription every day, again and again, proves difficult for many. Yet there are few diseases where strict adherence is as important as in HIV infection [Paterson 2000]. Lapses may lead to rapid development of drug resistance, which not only undermines the efficacy of the current regimen, but – because of cross resistance among drugs – is also likely to compromise that of future regimens. Second, in 1998, after a few years of care-free prescribing, it became apparent that chronic use of antiretrovirals is often associated with development of chronic toxicity, such as the disfiguring lipodystrophy syndrome [Carr and others 1998]. Use of particular antiretroviral agents in addition may lead to a rise of blood lipid levels to such an extent that an increased risk for cardio-and cerebrovascular morbidity and mortality may be feared for [DAD 2004]. Particular antiretrovirals are toxic to mitochondria, the energy power houses of the cell, and may cause nerve and muscle damage, and, in the worst case, deadly liver failure [Brinkman and others 1999]. In summary: the success of HAART comes at a price. This should not let us lose sight of the fact that the benefits of HAART still far outweigh the disadvantages, but it has undoubtedly led to a certain reluctance to be very aggressive in starting antiretroviral therapy. Therapy is now generally initiated later in the course of infection than a few years ago and therapy guidelines have been modified accordingly [Yeni and others 2004].
The success of a particular antiretroviral regimen is directly dependent on the number of active drugs in that regimen. Unfortunately there is a growing population of HIV-infected patients who harbour virus with resistance to one or more currently available antiretroviral agents [Richman and others 2004]. Usually the drug resistance mutations have been acquired during periods of suboptimally suppressive therapy, but patients may also be infected with drug-resistant strains [Little and others 2002]. For a substantial proportion of patients it has become difficult or impossible to constitute antiretroviral drug regimens that will give sufficient and durable suppression of viral replication. Somewhat surprisingly these people are often still doing better on “failing” drug regimens than without antiretrovirals. Viral resistance mutations may be associated with loss of viral fitness, in other words they may make the virus less virulent. In such cases, despite the virological failure, decline of immune function may be relatively slow. Nevertheless, apart from dealing with the chronic toxicity, finding ways to treat patients with drug-resistant viruses, today is the major challenge of antiretroviral therapy. Fortunately, over the past few years patient adherence has been made easier by the development and appearance of greatly simplified regimens, comprising only a few pills a day. Single-pil, once a day fixed-dose combinations (FDCs) of first rate HAART regimens are being developed. Dealing with hepatitis virus co-infections forms an increasing challenge in the HIV-infected population. Substantial proportions of patients have co-infections with either hepatitis C or hepatitis B virus. In the developed world, the relative contribution of liver-related mortality to mortality of HIV-infected subjects has risen greatly in the HAART era [Bica and others 2001, Macias and others 2002]. This may be explained partially by a decline in traditional opportunistic disease
manifestations, but is also due to the fact that the prolonged survival of HAART-recipients allows the natural history of the hepatitis virus infections to take their course.

Obstacles to scaling up antiretroviral treatment

It was unbearable that the benefits of HAART were initially restricted to just a tiny proportion of those infected, i.e. those living in the developed world. In the light of the devastation HIV is causing in developing countries, pressure grew to make HAART available there too. Since 2000 this has culminated in a number of important developments. Political commitment to include antiretroviral treatment as an essential component of the fight against HIV/AIDS increased greatly, both on an international and national level. Impressive price reductions for antiretrovirals for the poorest countries were negotiated between UNAIDS and research-based pharma, followed by further price reductions of a number of drugs through generic competition. WHO included antiretrovirals in the Essential Medicines list and formulated guidelines for the development of a public health approach to treatment of HIV infections in resource-poor settings [WHO 2002]. New and substantial funding mechanisms, such as the World Bank’s Multicountry AIDS Program (MAP), the Global Fund to Fight AIDS, TB and Malaria (GFATM), and President Bush’s Emergency Plan for AIDS Relief (PEPFAR) were established. And lastly, through its “3by 5” initiative, WHO’s set the target to have 3 million people in resource-poor settings on antiretroviral therapy by the end of 2005 [WHO 2002].

Due to the increases in resources, in global and national commitment, and the effect of WHO’s target setting, numbers of people in resource-poor settings who receive HAART have increased substantially over the past year. In fact, they have doubled between June and December 2004.
Despite the progress made, the reality on January 1 2005 however, was that out of the 4 million HIV-infected people in sub-Saharan Africa that needed to be treated with antiretroviral to prevent them from dying from AIDS within the next year or two, only about 325,000 (8%) were. A similar 8% figure applies to South and South-East Asia [WHO 2005]. It is also sobering to be reminded of the fact that although we are still far from meeting the “3by5” target, even if this target would be met, the number of new HIV infections occurring in 2005 would be approximately twice that of the people put on therapy.

There are still considerable obstacles to providing effective HIV therapy to all of those in need, which are listed in Table 1 and discussed here.

**Insufficient political commitment**

In some of the hardest hit countries, such as South Africa (with over 5 million HIV-infected people!), governments fail to recognize the scope and urgency of the problem, and may even exhibit erratic and counterproductive attitudes at the highest level that block the action that is so urgently needed. This does not only apply to treatment, but also to prevention. In a country like Russia where the HIV incidence is high, but the prevalence is still so low that there is an opportunity to stem the emerging epidemic by rational government action, the national leadership is remarkably silent and passive about HIV/AIDS and its repressive attitudes actually fuel new infections [UNAIDS 2004].

**Cost of care, including antiretrovirals**

Health care budgets of sub-Saharan African countries are generally extremely low, with annual per capita spending often being less than $ 20. The annual cost of even the cheapest available
HAART regimen for the poorest countries currently is around $150, and in many settings this low price is theory rather than reality. So for a long time the HAART scale up will be dependent on substantial contributions from the international donor community. Middle income countries form a specific problem, because they do not qualify for similar drug price reductions as the least developed countries, making governments reluctant to initiate large antiretroviral treatment programs. However, we should also recognize the fact that governments make choices, and can only applaud the shining example of Brazil, where the government, after succumbing to pressure from civil society, has managed to provide effective universal free access to HAART to its HIV-infected population [WB AIDS supplement 2004]. Similar engagement and pressure from civil society is lacking in many African countries.

Cost-considerations have favoured widespread use of a particular generic fixed dose HAART combination in sub-Saharan Africa. In the light of the emergency situation and the drive to put as many people as quickly as possible on treatment, this is understandable, but the long-term costs of this “cheap” choice should not be ignored. In the developed world, nobody today would initiate such therapy. Although the short-term tolerance of this regimen is generably good, after a few years of treatment a majority of people will develop a disfiguring syndrome of body fat redistribution, with complete loss of facial fat [Van der Valk 2004]. Apart from the (avoidable!) human suffering this will cause, it will certainly have a negative impact on antiretroviral uptake and it would be wiser to spend a bit more money on better HAART regimens.

**Lack of infrastructure, lack of expertise**

Even before the HIV/AIDS epidemic the public health sector in sub-Saharan Africa was very much underresourced, with limited possibilities to diagnose, prevent and treat many of the diseases that abound, including those of non-infectious origin, such as hypertension, diabetes
mellitus and stroke. Because of poor working conditions and low salaries, retention rates of doctors and nurses in the public sector in many sub-Saharan countries are appallingly low [ref]. The HIV/AIDS epidemic has not only greatly increased demands on an already malfunctioning health sector, but also further attenuated the work force by its lethal effect on infected health care workers. Among the already low numbers of health care workers available, few have expert knowledge about the treatment of HIV infection. This does not only apply to sub-Saharan Africa, but also to a number of Asian countries [Treat Asia Report 2004].

**Lack of a common agenda and leadership in implementation**

It has taken the world a long time to arrive at its current level of commitment to fight HIV/AIDS, but we are not where we should be yet. The HIV/AIDS epidemic represents a challenge of immense complexity and asks for an exceptional response. To paraphrase Jean-Francois Rischard: it is one of those inherently global problems that are getting out of hand in an exponential way, whereas the traditional way of working of human institutions is along a linear time scale (the clash between “dog years” and “bureaucratic years”) [Rischard 2002]. Despite the increased sense of urgency regarding the tackling of HIV/AIDS and the increased resources for it, we still do not have the undisputed global leadership and common agenda with a clear division of tasks that is so needed to cope with the “implementation gap”. In fact, in many countries, donors and technical assistance agencies are falling over each other, often in clear competition with each other.

No single existing organization, institution or program is fit to fill the leadership gap. Multilateral organizations like WHO and the World Bank have pivotal roles to play, but certainly in the case of WHO, are inherently unable to deliver what is (unrealistically) expected from them, because of lack of resources, the inability to bypass an ineffective public sector, and the
multisectorality that is required for an effective response. The Global Fund suffers from insecurity of long-term funding prospects. Moreover, despite the intention to involve multiple stakeholders and delivery mechanism and bypass government dominance, it has thus far been unable to channel money to the private sector that could make a pivotal contribution to scaling up access to antiretroviral therapy in sub-Saharan Africa [GFATM website]. In addition, I doubt whether it is a good idea that it functions solely as a funding mechanism and has no implementation and technical assistance capacity, especially in the light of the relative lack of coordination among agencies. PEPFAR, through a well-funded and targeted approach, which builds partnerships between organizations that can provide technical assistance and developing country governments, is putting impressive numbers of people on antiretroviral therapy in a short time. As an example, figure 2 gives us the number of people screened and put on antiretroviral therapy in less than a year’s time in a PEPFAR funded program of the Ministry of Health of Zambia, in collaboration with the University of Alabama [Stringer 2005]. At the same time, PEPFAR, driven by the current US unilaterism, operates in relative isolation of the other global players, and thus far has only paid lip-service to building public-private partnerships in countries. Lastly, although EU countries contribute considerable amounts of money to the global fight to HIV/AIDS, the EU is invisible because of the usual fragmentation.

Overcoming the obstacles

If it took a large concerted global effort, with clear divisions of tasks and accountability, to eradicate smallpox [Eradication of smallpox book], how can it take less than that to tackle an infinitely more complex challenge like bringing HIV/AIDS under control? A disease that thrives on the many wrongs of societies, poverty, inequality, stigma, for which unfortunately there is no simple fast fix. A disease, that, if treated, requires lifelong care, which requires
sustainable and effective health systems. A disease that mainly affects those in the prime of their lives, further contributing to poverty and undermining an effective response. The magnitude, multisectorality and complexity of the effort that is needed ironically are an obstacle to the global leadership, coordination, planning and coalition building that are also very much needed.

Nevertheless, we cannot afford to continue to do business as usual. We cannot afford not to treat those who need to be treated with antiretrovirals. We cannot afford to continue to debate the relative merits of prevention versus treatment. This is a false dichotomy; we desperately need long-term strategies, but if we don’t fight the battles of today, keeping people with HIV infections alive, future battles will only become more difficult.

We need to massively train health care workers to make them more effective in fighting HIV/AIDS, but in the short-term we can never train enough of them to deal with the tasks required. We thus also need to explore novel mechanisms of care delivery by non-physicians, such as community-based observed therapy (DOT) [Farmer]. Above all, we need to retain the health care workers that have been trained. Thus we need to recognize economic realities on the ground and bypass government restrictions on remuneration of those working in the public sector. The eventual cost of not doing so will be far higher than immediate implications for health care budgets. We also need to make far more us of the private sector in delivering health care and not exclude it from receiving donor money.

The principle of “what works” should prevail over the (questionable!) notion of what constitutes an “ideal society”. How come billions are invested in the telecom, beverage and oil industry in sub-Saharan Africa and not in the health industry? Could it be that the oil and telecom industry is allowed to make a profit? Why is it that we are always talking about the problem of drug
distribution when there is virtually no place in Africa where one cannot get a cold beer or a cold Coca Cola? Martin Wolf catches it in one sentence: “The sight of the affluent young of the west wishing to protect the poor of the world from the processes that delivered their own remarkable prosperity is unutterably depressing.” [Wolf 2004]. Why is so little effort directed at building sustainable financing mechanisms for health care for the masses? This would take the establishment of robust insurance schemes by reliable institutions, thus not necessarily the states. Why isn’t part of the Global Fund or other donor money used to kickstart these?

There has been criticism of the current “vertical approach” to scaling up antiretroviral therapy, draining away scarce health sector resources for other diseases, but people should realize that by nature of the chronicity and manifold manifestations and ramifications of the disease, a vertical HIV treatment program rapidly becomes a horizontal program. I like to believe that the current momentum for the antiretroviral scale-up provides a unique opportunity to empower the poor and build sustainable health care systems in Africa and other resource-poor settings.

References (to be shortened and completed)


Rischard JF. High Noon


UNAIDS 2004


Table 1

Insufficient political commitment
Cost of care (including antiretrovirals)
Lack of infrastructure
Lack of expertise
Lack of a common agenda and leadership in implementation