Consensus Statement on Antiretroviral Treatment for AIDS in Poor Countries

By

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(Signatories at end)

Overview: The worldwide AIDS pandemic continues to gather force. An estimated 36 million people are infected with HIV and face disease and early death unless they receive appropriate life-extending medical care. In addition to tremendous human suffering, the pandemic has become a major cause of social, political and economic instability. In wealthy countries, there has been dramatic success in the fight against HIV/AIDS, success that has been largely achieved through the use of antiretroviral therapy. Those with access to this treatment have enjoyed tremendous gains in survival and quality of life. Yet despite this success, antiretroviral therapy remains largely inaccessible in the world's poorest countries, where interventions have focused almost exclusively on prevention. With soaring death rates from HIV/AIDS in low-income countries, both the prevention of transmission of the virus and the treatment of those already infected must be global public health priorities.

Past objections to AIDS treatment in poor countries fall into several categories. First, poor countries lack the adequate medical infrastructure to provide AIDS treatment safely and effectively. Second, difficulties with adherence to complicated medication regimens would promote and spread drug resistance. Third, antiretroviral drugs are expensive, and the treatment cost is too high for the United States and other wealthy countries to finance without siphoning resources away from HIV prevention programs and other worthy development goals. Finally, commitment from political leaders in Africa and other poor regions is not sufficient to underpin a major international effort towards providing AIDS treatment.

As signers of this Consensus Statement, we believe that the objections to HIV treatment in low-income countries are not persuasive and that there are compelling arguments in favor of a widespread treatment effort. Falling prices of anti-retroviral drugs have dramatically altered the economics of HIV treatment, and obstacles to treatment such as poor infrastructure can be overcome through well-designed and well-financed international efforts. Appropriate treatment can not only prevent infected individuals from succumbing to life-threatening illness from AIDS but may play a major role in prevention both by reducing the viral load of those under treatment and by encouraging greater participation in prevention programs. A considerable body of evidence suggests that effective AIDS treatment is now possible in low-income countries. Through large-scale, scientifically monitored programs, the development and sustainability of highly effective AIDS treatment strategies remains promising in settings of poverty and high AIDS prevalence.

[1] This document represents the views of the individual signatories and should not be construed as representing official views of Harvard University or of any institutions within the University.

We believe that on moral, health, social and economic grounds the international community should provide the scientific and financial leadership for a rapid scaling-up of AIDS treatment in the poorest and hardest-hit countries of the world. Initial efforts should be focused on those with more advanced HIV infection, with a target of at least 1 million AIDS patients in Africa in treatment within 3 years as a first objective, and indeed more if feasible, and with a proportionate scaling up in hard-hit countries in other parts of the world. [2]

[2] Africa accounts for around 80 percent of all HIV-infections in low income or high prevalence countries. As of end-1999, UNAIDS estimates that 24.5 million of Sub-Saharan Africans were living with HIV infection. With minimal exceptions, those countries were either low-income (<$755 per year), or high prevalence (>2 % of adults infected, for purposes of our discussion) or both. There are roughly 5 million more HIV-positive individuals in low-income or high-prevalence countries outside of Africa, including 4.7 million in South and Southeast Asia (of which 3.7 million are in India), and around 350,000 in the Western Hemisphere (mainly Haiti and the Dominican Republic).

Introduction

Twenty years after HIV/AIDS was first diagnosed, it has become the modern world's greatest pandemic. AIDS has taken 22 million lives and created more than 13 million orphans.[3, 4] It is the only disease with its own United Nations office, UNAIDS, and yet this and other global efforts have been ineffective in preventing the further spread of the disease. Closely related subtypes (or clades) of HIV are responsible for multiple concurrent epidemics that are beginning to appear beyond their initial geographic borders. An estimated 16,000 new infections occur every day worldwide, and based on current trends, AIDS deaths will exceed those associated with the Black Plague of the 14th century by the year 2004. In the end, no country will escape the disaster. The disease not only has weakened the social, political, and economic fabric on local, regional, and national levels but also promises to fundamentally destabilize this fabric worldwide.

Until a few years ago, HIV infection led almost inevitably to an early death from AIDS. However, in the mid-1990s, the HIV/AIDS community saw a scientific breakthrough through the development of highly active anti-retroviral therapy (HAART), a treatment "cocktail" of antiretroviral drugs. Since the advent of HAART, the disease has been transformed into a treatable and chronic condition for a significant proportion of those with access to this treatment. Yet 95 percent of the 36 million HIV-infected individuals in the world live in low-income countries, and only a tiny fraction of these people have access to HAART. A few middle-income countries, such as Brazil and Thailand, have achieved some level of coverage through bold and effective national policies.[3] In the much poorer countries of Sub-Saharan Africa and other affected parts of the world, HAART remains almost completely unavailable. It is estimated that only around 10,000 of Africa's 25 million HIV-positive individuals receive HAART. In Malawi, for example, just 30 persons out of 800,000 HIV-positive individuals currently receive HAART.[5]

As individuals committed to equitable access to health care for all peoples and to human rights, we have joined together to address the growing global need for AIDS treatment. This Consensus Statement, which draws upon widespread discussions within our academic community, addresses the reasons why antiretroviral therapy in poor countries is likely to prove feasible and effective, and how the barriers to providing life prolonging AIDS treatment can be overcome.

Why AIDS treatment is a global priority

Over the past two decades, the international response to HIV/AIDS in poor countries has emphasized HIV prevention, primarily due to the high cost of treatment and the limited resources available to developing countries. Despite this emphasis, the available scientific tools for

[3] UNAIDS. Report on the global HIV/AIDS epidemic. Geneva: UNAIDS, 2000. Available at http://www.unaids.org/epidemic_update/report/Epi_report.pdf.
[4] UNAIDS. AIDS Epidemic Update: December 2000. Geneva: UNAIDS, 2000. Available at http://www.unaids.org/wac/2000/wad00/files/WAD_epidemic_report.PDF.
[5] H.P. Binswanger. How to make advanced HIV treatment affordable for millions in poor countries. (In preparation)Dr. Binswanger is the President of AIDS Empowerment and Treatment International.

prevention, in the absence of effective vaccines, remain inadequate to stop the spread of the disease. The very mention of AIDS treatment has often been avoided by donor agencies in wealthy countries, for fear that raised expectations would increase the financial and operational demands upon them, and detract from prevention efforts. The disparity in access to effective treatment between wealthy countries and developing countries is neither scientifically nor ethically justified at this time.

We believe that the extension of proven effective medical care to the millions of people suffering from HIV infection in the poorest countries of the world is an urgent priority, and that programs to prevent HIV transmission and to deliver effective medical treatment to those stricken by AIDS can and must go hand in hand.

There are at least 4 compelling reasons for combining AIDS prevention and treatment:

1. *Treatment is essential to the 36 million people already infected with HIV, the vast majority of whom will die of AIDS without it.* This is the immediate humanitarian rationale for treatment. The pandemic has already claimed 22 million lives, including 17 million in Africa [6].

2. *Treatment is necessary to optimize prevention efforts.* When treatment is not available, less incentive exists for an individual to take an HIV test, since HIV-positive status not only is associated with social stigmatization but also is tantamount to a death sentence. It is only when HIV testing is coupled with treatment that people have an incentive to be tested, thus enabling a rational response to AIDS: primary prevention for those who are HIV uninfected, and antiretroviral treatment for those who are HIV infected. Effective antiretroviral treatment of HIV-positive people also lowers the viral load within infected individuals, which in turn has a major effect in reducing the likelihood that they will transmit HIV infection to others. [7] [8] [9] Ultimately, then, appropriate treatment of infected individuals may become a major tool in AIDS prevention.

3. *Treatment is necessary to save the children -- and fabric -- of societies.* Without treatment, the number of adult deaths expected from AIDS is so great that the currently catastrophic figure of 13.2 million AIDS orphans will grow into an even more socially devastating wave in coming years (by some estimates, 44 million orphans of all kinds by 2010).[3,10] Without family support, these children often can not attend school, suffer from poverty and malnutrition, and become victims of violent and sexual crimes—all of which places them at high risk for acquiring AIDS and which threatens to mire them in increasingly desperate conditions.[3] If the current lack of treatment continues, a demographic shift is predicted in the most severely afflicted parts of Africa such that teenagers will outnumber their elders by

[6] AIDS Epidemic Update: December 2000; available at www.unaids.org.
[7] UNAIDS (1999). HIV/AIDS prevention in the context of new therapies. (UNAIDS, Geneva)
[8] C. Hart *et al*. (1999). Correlation of human immunodeficiency virus type 1 RNA levels in blood and the female genital tract. *J Infect Dis* 179:871-882.
[9] P. Vernazza *et al*. (2000). Potent antiretroviral treatment of HIV infection results in suppression of the seminal shedding of HIV: the Swiss Cohort Study. *AIDS* 28:117-121.
[10] USAID. Children on the Brink: Updated estimates & recommendations for intervention. USAID: 2000. Available at http://www.usaid.gov/press/releases/2000/childrenreport.pdf.

2020.[11] This demographic shift may contribute directly to increase political instability and violence

4. *Treatment is necessary for continuing economic development.* Without treatment, millions of adults in the prime of their working lives will die of AIDS and take with them the skills and knowledge base that are necessary for human and economic development.[12] For example, in Zambia teachers are dying of AIDS almost as quickly as they are trained.[13] The loss of skilled workers is a major reason why AIDS will seriously reduce the rates of future economic growth.[14] The goal of simply preventing new HIV infections, without simultaneously offering treatment to prolong the lives of those already infected, has proved insufficient to appreciably mitigate these trends.

Despite these arguments and despite the proven efficacy of presently available therapies, antiretroviral drug treatment remains inaccessible to most of the world's infected population.

HIV Treatment in High-Income Countries

Partially effective treatment for HIV-infected individuals was first introduced in 1986. Zidovudine (AZT), the first antiretroviral drug used for treating HIV infection, was shown to reduce both deaths and the disease's accompanying opportunistic infections in individuals with advanced HIV infection.[15] For the next several years, incremental advances were made with the discovery of other antiretroviral drugs, including didanosine (ddI), lamivudine (3TC), and stavudine (d4T) among others. However, the benefits of single drug treatments were relatively short-lived; treatment failures often occurred within months to a few years and usually were associated with the emergence of viruses resistant to the very drugs used to fight them.

A conceptual breakthrough occurred when it was shown that combining two or three antiretroviral drugs in "cocktail" regimens could delay the emergence of drug resistance and lead to a more profound and prolonged benefit than could individual drugs.[16] [17] [18] New classes of drugs, the protease inhibitors and non-nucleoside reverse transcriptase inhibitors, allowed for

[11] Monitoring the AIDS Pandemic Network. The Status and Trends of the HIV/AIDS Epidemics in the World, 2000. U.S. Census Bureau, 2000.
[12] R. Bonnel (2000). HIV/AIDS: Does it Increase or Decrease Growth in Africa? (Mimeo. World Bank: Washington).
[13] UNICEF. The progress of nations 2000. New York: UNICEF, 2000.
[14] R. Bonnel (2000). HIV/AIDS: Does it Increase or Decrease Growth in Africa? (Mimeo. World Bank: Washington).
[15] M. Fischl et al, The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trialNEJM 1987; 317:192-197
[16] S. Hammer et al, A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study TeamNEJM 1996: 335:1081-90
[17] S. Hammer et al, A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 StudyNEJM 1997;337:725-733
[18] M. Hirsch et al, A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapyJ Infect Dis 1999; 180:659-665

more potent three-drug antiretroviral regimens. These regimens, known highly active antiretroviral therapy (HAART), have resulted in the reduction of HIV levels in the blood, often to undetectable levels, and have markedly improved immune function in HIV-infected individuals.[19]

The advent and widespread application of HAART has dramatically changed the typical course of HIV infection and AIDS. Once almost uniformly deadly, HAART has transformed HIV infection into a chronic condition that frequently remains without symptoms for many years, with resultant gains in life expectancy. Moreover, with the ability of HAART to dramatically decrease viral replication, the chance of transmitting the virus has diminished correspondingly; indeed, antiretroviral drugs administered during labor and delivery have dramatically reduced (by well over 50%) maternal–to-newborn transmission of HIV, saving thousands of infants from the complications and early death associated with AIDS.[20] Coincident with the introduction of these therapies, AIDS death rates during the past six years have plummeted in the United States and other wealthy countries (Figure 1).

Current U.S. government recommendations suggest treatment of all individuals with moderately advanced to advanced HIV infection using HAART regimens of three or more antiretroviral drugs.[21] Recommendations in other high-income countries are similar.[22,23] Although these drug regimens all have associated side effects, inconvenience and high cost, improvements have already been made to develop less toxic, more convenient fixed-dose combination tablets and cheaper treatment regimens. As a result, it is reasonable in 2001 to expect people diagnosed relatively early in the course of HIV infection to live long and productive lives. Finally, recent cost effectiveness studies indicate that HAART represents a highly cost-effective medical intervention, comparable in quality-adjusted years of life to treatment of hypertension.[24]

HIV Treatment in Low-Income Countries

The picture of success and continued improvement in the prevention and treatment of AIDS in high-income countries is in stark contrast to what has been seen in low-income countries. In the low income countries, the overwhelming proportion of HIV-infected persons have no access to HAART. In sub-Saharan Africa, for example, this lack of treatment access has translated into rapidly escalating death rates (Figure 1). A few middle-income developing countries, notably

[19] C. Carpenter et al., Antiretroviral therapy in adults: updated recommendations of the International AIDS Society-USA Panel JAMA 2000;283:381-390

[20] Perinatal HIV Guidelines Working Group (2001). Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States. Available at: http://www.hivatis.org/guidelines/perinatal/Jan24_01/PERJAN01.PDF.

[21] Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation (2001). Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. Available at: http://www.hivatis.org/guidelines/adult/Feb05_01/pdf/AAFEB05B.PDF.

[22] British HIV Association Writing Committee (2000). British HIV Association Guidelines for the treatment of HIV-infected adults with antiretroviral therapy. Available at: http://www.aidsmap.com/bhiva/bhivagd1299.htm.

[23] J. Delfraissy. Prise en charge thérapeutique des personnes infectées par le VIH. (Paris: Flammarion, 2000).

[24] K. Freedberg *et al.*(2001). The Cost Effectiveness of Combination Antiretroviral Therapy for HIV Disease. *NEJM* 344:824-831.

Brazil and Thailand, and more recently Costa Rica, have introduced HAART successfully within nationally funded programs; however, these countries have approximately 10 times the per capita income of the poorest countries and roughly one order of magnitude lower HIV prevalence. The lack of feasibility studies in poorer countries has impeded the widespread dissemination of HAART to many of the places where it is needed most.

Nevertheless, HAART has been delivered successfully in poor settings. One example is the Harvard-affiliated Clinique Bon Sauveur in Haiti, established by Partners in Health in the middle of a squatter settlement of persons displaced by a hydroelectric dam. Starting in 1998, HAART was made available to a small number of late-stage AIDS patients, whose disease no longer responded to the treatment of opportunistic infections. In the Harvard-Haiti protocol, HAART is prescribed to patients based on easily observed clinical signs and symptoms, rather than advanced laboratory tests, such as CD4 cell counts and viral load, which are not currently available in this poor and rural setting. The guidelines for initiation of HAART in this program include the following:

- Absence of active tuberculosis
- Recurrent opportunistic infections that are difficult to manage with either antibacterial or antifungal drugs
- Chronic diarrhea with wasting
- Unexplained and significant weight loss
- Severe neurologic complications attributable to HIV
- Severe lowering of red and/or white blood cell counts

One of the key arguments against AIDS treatment in low-income countries is the belief that patients will fail to take antiretroviral drugs consistently and therefore, not only will become resistant to these drugs but also transmit resistant virus. To ensure that patients take antiretroviral drugs regularly, the Harvard-Haiti protocol dispenses drugs using the principles of directly observed therapy (DOT), which have been demonstrated to be effective in treating tuberculosis and reducing the emergence of drug resistant strains. Each HIV-infected patient is assigned an *accompagnateur*, (a "companion", most often a community health worker) who observes ingestion of the HAART medications daily and offers support to the patient and family. Directly observed therapy of HAART (or DOT-HAART) ensures that the HIV-infected patient is taking medications regularly, and this promotes the best clinical outcome for the patient and minimizes the opportunities for drug resistance to develop.[25] Dozens of patients have been enrolled in the Harvard-Haiti project, and all have had a positive clinical response, characterized by weight gain and the abatement of AIDS-related symptoms, and the medications have been well tolerated.[26]

[25] Improvements in clinical outcomes due to DOT-HAART, compared with self-administered therapy (SAT) were reported in U.S. trials. M. Fischl, et al, "Impact of Directly Observed Therapy on Long-Term Outcomes in HIV Clinical Trials," Abstract 528, 8th Conference on Retroviruses and Opportunistic Infections, Chicago, February 4 – 8, 2001, at http://www.retroconference.org.

[26] P. Farmer, et al, "Community-Based Approaches to HIV Treatment: DOT-HAART in Resource-Poor Settings" Lancet (in press, 2001)

The DOT model for delivery of HAART is particularly compelling for several reasons. First, a widespread, successful global infrastructure has already been established for DOT-based tuberculosis treatment programs,[27,28] through which HAART might be effectively delivered. Second, substantial overlap exists between those infected with tuberculosis and AIDS, since tuberculosis is the major opportunistic infection of HIV disease in poor country settings. Third, DOT is cost-effective (i.e., an efficient use of limited resources) in poor, low-wage settings, as it is labor- rather than resource- intensive and requires only community workers with little training. Fourth, the tight control of drug dispensing in DOT blocks the development of a black market in antiretroviral drugs. This matter, in particular, is of considerable importance to those seeking efficacious AIDS treatment as well as to pharmaceutical companies, who need protection from a black market when providing drugs at deeply discounted prices.

HAART delivery in poor settings has not been limited to Haiti. Both Senegal and Côte d'Ivoire have seen successful distribution of HAART.[29,30,31] In Senegal, 86 patients have been treated in a pilot program for over two years. These studies show that persons in poor countries are able to adhere to medications and that AIDS treatment can be successfully delivered. Based on clinical trial data from developed countries, there is ample reason to expect that AIDS treatment in these settings will result in similarly significant gains in extending life and health.

Proposal for Treatment of HIV Infection in Poor Countries

We hypothesize that the widespread treatment of AIDS with HAART in the world's poorest countries is both feasible and effective, and urge that this hypothesis be tested immediately. We propose that broad availability of HAART be phased in over the next 3-5 years through simultaneous, large-scale pilot programs designed to determine the best treatment strategies for use in poor countries. These pilot programs would provide treatment immediately, while concurrently maximizing adherence; limiting the development of drug resistance; utilizing existing infrastructure; building new infrastructure; and monitoring drug flow to ensure compliance of drug distributors with international agreements on discounted pricing and carefully controlled distribution. A proportion of the persons receiving treatment in these programs would also enroll in intensive clinical trials, which would collect state-of-the-art virological, immunological, and clinical information; this information, such as CD4 cell counts and viral loads, would optimize treatment protocols and determine treatment efficacy through scientific methodology. We also emphasize the importance of full local involvement of HIV-infected communities in the design and implementation of treatment and trials. Large-scale pilot

[27] M. Desvarieux *et al*. (2000). A novel approach to directly observed therapy for tuberculosis in an HIV-endemic area. *Am J Public Health* 91:138-41.
[28] P. Kamolratanakul et al, (1999) Randomized controlled trial of directly observed treatment (DOT) for patients with pulmonary tuberculosis in Thailand. *Trans R Soc Trop Med Hyg* 93:552-7.
[29] P. Sow, "Clinical, Immunological and Virological Effectiveness of Antiretroviral Therapy in a Resource-Poor Setting: The Senegalese Experience" Abstract 490, 8th Conference on Retroviruses and Opportunistic Infections.
[30] R. Landman, et. al., "Evaluation at 6 months of a Once-a-Day HAART Regimen in Treatment-Naive HIV-1-Infected Adults in Senegal (ANRS 12-04 Study)" Abstract 491, 8th Conference on Retroviruses and Opportunistic Infections.
[31] Y. Diop, et al, "Prospective Trials of CBV + IDV in West Africa" [Cote-d'Ivoire], Abstract 492, 8th Conference on Retroviruses and Opportunistic Infections.

programs, coupled with scientifically rigorous clinical studies, would not only make treatment available immediately, but would gather the critical data necessary to improve future treatment. It is only through these efforts that we can address the most critical questions regarding widespread AIDS treatment in resource-poor settings.

1. Who should be treated?

Recent guidelines in developed countries, based in part on cumulative toxicities of the antiretroviral drug regimens, recommend deferral of HAART until the later stages of HIV infection and that treatment be guided by laboratory tests such as CD4 cell count and viral load. Current U.S. guidelines, for example, recommend initiating HAART at CD4 counts less than 350 cells/mm^3 or viral loads greater than 30,000 copies /ml of plasma [32] While the optimal timing of therapy in resource poor nations has not been studied, starting treatment in the later stages of disease makes practical sense. It is those late in the course of the disease whose survival time is most enhanced by HAART and who are most easily identified as candidates for treatment on the basis of clinical signs and symptoms, even without facilities to perform CD4 or viral load testing.

However, as with other aspects of scaling up HAART, who should be treated, and when, are questions for clinical, epidemiological, and operational research to answer. That is, all large-scale efforts to provide AIDS treatment should be carefully monitored and designed to reap the maximum benefits, and the maximum amount of information regarding the efficacy of the proposed protocols. This said, we recommend treatment for HIV-infected individuals as follows:

(a.) Multiple pilot programs, including a subset of the population in clinical trials, should be initiated in parallel in different locales, since the logistics of drug delivery and response to therapy may vary from place to place. All programs, and especially the clinical trials, should be supported by the public scientific institutions of wealthy countries (e.g. the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and their counterparts in other countries), UNAIDS, and academic research centers.

(b.) Among the planned programs, consideration should be given to rapidly starting a several large-scale countrywide trials, to be conducted initially over a period of about three years. Trials of this breadth are essential for assessing the feasibility of country-scale AIDS treatment, with a view to overcoming a range of possible barriers. The countries in which these trials are conducted should be selected based on strong governmental support and some existing infrastructure to back the effort. With adequate infrastructure development and support as part of the programs (discussed below), such trials could enroll several tens of thousands of patients within a country, or what might be a sizeable fraction of the AIDS patients in a small country.

(c.) In areas *with* access to CD4 counts and/or viral load testing, selection of persons to treat should be based on these laboratory measurements and should initially use the treatment guidelines accepted in wealthy countries. The outcome of treatment based

[32] Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation (2001). Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. Available at: http://www.hivatis.org/guidelines/adult/Feb05_01/pdf/AAFEB05B.PDF.

on these selection criteria and guidelines should be rigorously assessed as experience accumulates to bring improvements to future treatment decisions.

(d.) In areas *without* access to CD4 counts or viral load testing, selection of persons to treat should be based on HIV seropositivity and AIDS-defining clinical signs and symptoms. To ensure that symptom-based treatment does not compromise timely treatment, studies should be done to correlate the clinical criteria with laboratory-based CD4 and viral load measurements, which could be furnished by a network of international reference laboratories (discussed below).

(e.) Consideration should be given to designing pilot programs and clinical trials to treat both adults and children.

(f.) Consideration should be given to designing pilot programs to contribute directly to preventing the spread of infection. For purposes of prevention, particular groups that should be targeted include HIV-infected pregnant women, and groups involved in high-risk behavior for transmission. Such programs would promote and assess the potential role of HAART in reducing the transmission of HIV on a population scale.

(g.) Since tuberculosis is the major cause of death in persons with AIDS, treatment for tuberculosis should be available to protect both HIV-infected individuals and to prevent their transmitting tuberculosis to their family members and close contacts.

2. What treatments should be used, and how should they be delivered?

With many antiretroviral drugs on the market, a large range of HAART regimens are available in wealthy countries. The ideal regimen should be potent and well tolerated; should have low drug toxicity; should be simple for the patient to take; and should not be prone to development of drug resistance. There are as yet no proven data that one particular regimen is best for initiating therapy, and therefore, several treatment regimens should be available for use in poor countries. In addition, almost all treatment data have focused on HIV subtypes prevalent in the U.S. and Europe. No data exist to indicate which antiretroviral regimens are optimal for treatment of the most globally prevalent HIV subtypes, such as HIV-1C.

Ultimately, operational rather than biomedical considerations may make one regimen preferable to another. Complicated treatment regimens often require multiple drugs to be taken at different times throughout the day. The recent development of new, fixed-dose combinations, which combine several antiretroviral drugs in a single tablet, can help make HAART easier for the patient to take and thus can help forestall the development of resistance. Brand name products such as Trizivir (GlaxoSmithKline) already combine three drugs (zidovudine, lamivudine, and abacavir) into a single tablet taken twice daily, and forthcoming products from a generic manufacturer (Cipla) will combine other drug combinations (zidovudine, lamivudine, and nevirapine; and stavudine, lamivudine and nevirapine) into a single tablet with similarly simple dosing.[33] In addition, several currently available drugs (e.g., didanosine, efavirenz) and others in development (e.g., tenofovir, emtricitabine, and BMS 232,632) can be administered once daily, and this holds out the prospect of once-daily HAART regimens. A DOT-HAART regimen taken once daily would make possible a high level of patient adherence to drug treatment as has previously been seen in well-run, DOT-based tuberculosis treatment programs in poor countries.[30,31]. This approach could also be augmented through small cash incentives or through

[33] Personal communication to the authors, Dr. Y.K. Hamied, Cipla Ltd. (March 2001).

recruitment of health workers from the community, both of which have been shown to improve adherence.[34]

In summary, simplified dosing regimens of antiretroviral drugs, combined with direct observation and/or other strategies to improve patient adherence to medication are likely to be effective in poor countries. We accordingly recommend the following:

(a.) HAART regimens should be chosen based on established efficacy, safety, ease of administration and tolerability.
(b.) DOT programs should be formally evaluated and compared to other treatment delivery and patient monitoring programs.
(c.) Treatment proven to be sub-optimal in wealthy nations, such as the use of only one or two nucleoside inhibitors, should not be used.
(d.) DOTS treatment for tuberculosis should be integrated into the treatment protocol for those persons infected with both HIV and TB.
(e.) An expanded effort to track the development of antiviral drug resistance has to be part of clinical trials

3. Where should treatment be administered?

International support for treatment should be made available in any resource poor country where there is political support locally and at the highest levels for providing access to AIDS treatment on a scientifically monitored basis. The international community should be prepared to reciprocate this interest with technical and financial assistance to build the needed infrastructure for treatment and monitoring. The existing local infrastructure and resources would determine the type of treatment and methods of monitoring that are initially used: e.g., treatment based on CD4 cell counts and/or HIV viral load monitoring, or treatment based on symptomatic illness, such as in the Harvard-Haiti protocol. In those areas where existing treatment infrastructure is lacking, this should not be cited as an impasse by which to forego treatment. Efforts should be initiated to build the clinical and diagnostic capacity to furnish and monitor therapy, making use in the interim of geographically distant infrastructures (including those in wealthy countries) to monitor the efficacy of interventions and the potential adverse effects of the antiretroviral drugs. Research efforts also should be directed toward understanding how different levels of locally available laboratory infrastructure affect therapeutic outcomes, and whether alternative, lower-cost technologies for CD4 cell count and viral load testing are useful and reliable in poor countries.[35] We accordingly recommend the following:

(a) International support for treatment should be made available in all low-income or high prevalence nations where there is political support locally and at the highest levels for providing access to AIDS treatment on a scientifically monitored basis.

[34] J. Volmink and P. Garner (2001). Interventions for promoting adherence to tuberculosis management (Cochrane Review). Issue 1, 2001. Oxford: Update Software.
[35] The WHO has collected information on alternative CD4 and viral load measurement technologies that are both established and less expensive than those customarily used in wealthy countries. A useful summary of these alternative technologies, with costs, is found in "Laboratory Requirements for the Safe and Effective Use of Antiretrovirals": http://www.who.int/HIV_AIDS/antiretroviral_modules/indexar.htm.

(b) Where the political will exists for treatment, the international community should assist in providing necessary infrastructure to support the rapid expansion of pilot programs for treatment, as well as the scientifically rigorous clinical trials that would accompany those programs.
(c) Until such time as all necessary infrastructure is in place, the local capacity to provide clinical and diagnostic support services, as well as treatment of tuberculosis and opportunistic infections should determine the type and intensity of the treatment programs instituted.
(d) The international community should redouble its aid effort to build the needed infrastructure, delivery capacity and monitoring capacity necessary to achieve the best therapeutic outcomes in poor countries without delay, once the precise infrastructure requirements are known.
(e) Efforts should be initiated immediately to expand education and training of health care providers and scientists from poor countries to support these efforts.

4. What diagnostic and supportive testing should be performed?

While AIDS treatment in resource-poor countries may necessitate different clinical guidelines and practices, acceptable practices must be instituted to ensure the safety and efficacy of treatment. This includes, for example, establishing standards for monitoring the clinical signs and symptoms suggestive of drug toxicity (e.g., jaundice, neuropathy). These will vary according to the drugs utilized and may include hematologic, renal, and hepatic assessments. Because different drugs have different toxicities, the monitoring standards and laboratory tests required in an individual situation should be determined by the HAART regimens utilized in a particular area.

In addition, where possible, blood should also be monitored for drug efficacy, as measured by increased CD4 cell counts and reduced HIV viral load, and where patients are not responding to therapy, for drug resistance. The frequency of such monitoring will vary over time. Initial response to therapy should be monitored by measuring CD4 cell counts and viral load at baseline and after several months of therapy. If viral suppression (i.e., treatment success) is achieved and maintained, monitoring frequency may be reduced. The role of viral resistance testing for individuals in whom regimens are failing is still being evaluated in wealthy countries and cannot be recommended for routine use in poor countries at this time. However, blood specimens should be stored, if possible, for eventual resistance testing, so studies can be conducted evaluating both the utility and cost-effectiveness of resistance testing in these settings. In summary:

(a.) Toxicity monitoring should be done by clinical examination and appropriate laboratory testing of blood specimens.
(b.) Specific laboratory tests and their frequency should be dictated by the HAART regimens being utilized.
(c.) CD4 cell counts and/or HIV viral load should be monitored at intervals, wherever possible, to assess the benefits of therapy.
(d.) Specimens should be stored for eventual studies evaluating the usefulness of viral drug resistance testing in resource-poor countries.

(e.) Clinical correlation between CD4 cell count and viral load with AIDS and opportunistic infections specific for each locale should be determined.
(f.) Efforts should be initiated immediately to develop less expensive monitoring assays, but this should not delay the implementation of treatment programs.

5. What questions should be asked in order to define the standard of care for AIDS treatment in resource poor settings?

The rapid expansion of treatment into resource-poor countries is necessary not only to provide life-prolonging therapies, but also to answer important questions that will improve future care. As in developed countries, clinical trials should define the "Best Practices" for AIDS treatment in poor countries and use them to develop treatment guidelines. The important scientific issues that should be addressed include the following:

(a.) Which HAART regimens are the best tolerated and have the lowest risk of adverse drug reactions requiring advanced medical care or immediate physician intervention, both of which are less likely to be available in poor countries?
(b.) Does the therapeutic outcome of HAART vary depending on whether a DOT protocol is used; and does it matter whether treatment is supervised by a lay person living in the patient's community or a more skilled health worker to whom a patient must travel?
(c.) What level of adherence to HAART can be achieved, and what social or programmatic factors can help promote the highest levels of adherence?
(d.) Does the therapeutic outcome of HAART vary according to treatment initiation based on clinical signs and symptoms of AIDS or treatment based initiation based on laboratory tests, such as CD4 cell counts or HIV viral loads?
(e.) Which symptomatic signs or inexpensive laboratory diagnostics most reliably predict when HAART should be initiated?
(f.) Does HAART efficacy and development of resistance vary according to the subtype of HIV that is being treated?
(g.) Does treatment for tuberculosis and other opportunistic infections enhance the effectiveness and sustainability of AIDS treatment?

Answers to these questions are vital to the systematic and rational improvement of AIDS treatment in poor countries. Rather than reject AIDS treatment because countries are too poor to adequately provide it, AIDS treatment must be performed differently in diverse settings due to constraints in infrastructure, skilled medical workers, and finance.

6. How should AIDS drugs be procured and treatment financed?

Financial arrangements for large-scale distribution of AIDS treatment should be based on three premises: (1) discounts and marketplace competition for AIDS drugs have reduced their price by 90% or more during the past year; (2) AIDS treatment will always be more expensive than poor countries can afford, meaning that international aid is key to financing the effort; and (3)

treatment should be offered in conjunction with greatly scaled up programs designed for prevention, since treatment and prevention must go hand in hand.

Last year, a number of the world's major pharmaceutical firms (Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Hoffman La Roche, and Merck) reached an agreement with UNAIDS to furnish antiretroviral drug therapy to poor governments at reduced cost.[36] This "Accelerating Access" initiative has led to agreements on price reductions in four countries—Cote d'Ivoire, Rwanda, Senegal and Uganda—with nearly twenty other countries in various stages of negotiations. In general, the Accelerating Access ground rules are that, in exchange for discounts of up to 90%, recipient countries pledge to respect patent rights and to institute safeguards that prevent the lower priced drugs from entering illicit, black market trade.

By early 2001, the Accelerating Access initiative had had little effect in scaling up AIDS treatment, even in the countries where price agreements were in force. Not only were the Accelerating Access prices still significantly above production cost (around $950 - $1,850 annually for a HAART regimen, depending on the specific "cocktail"), but they remained far too high for the impoverished countries to purchase out of their own resources or to provide the medical services needed for their effective delivery. In short without donor assistance the low-income countries have been unable to take advantage of these reduced prices.[37]

Prices have continued to fall rapidly in early 2001. As a result, several generic drug makers, most notably Cipla of India, have offered to supply generic products at prices lower than the Accelerating Access initiative.[38] In addition, two major pharmaceutical companies involved in the original initiative, Merck and Bristol Myers Squibb, have announced further, deeper price cuts to offer their drugs at or below production cost.[39,40] Similarly Abbott laboratories announded its decision to offer two antiretroviral drugs and a clinical test product in Africa at no profit[41]. Finally, Merck and GlaxoSmithKline have recently announced that they will sell discounted drugs not only directly to governments but also to non-governmental organizations and charities working in poor countries. These dynamic developments reflect the willingness of these companies to assist in this effort, various recent price quotations, and evidence on production costs, we estimate that a typical HAART regimen can cost $500 a year, and possibly less.[42]

While prices in this range are critically important and *necessary* to achieve a large expansion of AIDS treatment, they are not *sufficient*. Five hundred dollars per patient per year (patient-year) remains far above what most poor economies can afford without donor assistance. To illustrate,

[36] Other firms manufacturing antiretroviral drugs (e.g., Abbott), or offering other drugs useful for AIDS treatment (e.g., Pfizer) chose not to participate in this original agreement.
[37] M. Schoofs and M. Waldholz. Drug Companies, Senegal Agree To Low-Cost HIV Drug Pact. *Wall Street Journal* (October 24, 2000).
[38] D. McNeil. Indian Company Offers to Supply AIDS Drugs at Low Cost in Africa. *New York Times* (February 7, 2001). Cipla announced discounted prices of $350 (for Doctors Without Borders) and $600 (for governments) to purchase its versions of stavudine, lamivudine and nevirapine.
[39] H. Collins. Merck Cuts Prices for AIDS Drugs in Africa. *Philadelphia Inquirer* (March 8, 2001).
[40] M. Petersen and D. McNeil. Maker Yielding Patent in Africa For AIDS Drug. *New York Times* (March 15, 2001).
[41] Reuters, Abbott to Sell AIDS Drugs, Tests at No Profit in Africa, March 27, 2001.
[42] This is based on the raw materials cost of zidovudine, lamivudine and nevirapine, supplied to us by various manufacturers.

Ghana, Nigeria and Tanzania have a *per capita* gross national product (GNP) under $400; out of these funds, public-sector health budgets are $8/patient-year or less – far too little to deal with basic health needs, much less AIDS treatment.[43,44] Furthermore, obligations to pay foreign debt often outstrip the entire health budget in these countries. With AIDS poised to *reduce* the growth of income in these impoverished economies, it is virtually certain that additional loans taken on to deal with AIDS could never be repaid. The provision of international aid purely as grants, not loans, is therefore the only fiscally sound policy for such impoverished countries; and substantial grant support will also be needed for a few middle-income countries, such as South Africa and Botswana, where prevalence of HIV infection is high, so that the fiscal burden would once again be too large for the country to manage out of its own resources.[45]

Applying these current facts, we can approximate the amount of international aid that would be needed for a wide-scale AIDS treatment effort, using , for example, a DOT-HAART approach in a research setting in Sub-Saharan Africa (Annex A). Taking into account the costs of the drugs themselves, plus estimates for DOT operational costs, research to monitor and improve the effectiveness of HAART in the field, and associated material costs for clinical supplies such as diagnostic tests, we calculate the cost of DOT-HAART to be about $1,123/patient-year in Sub-Saharan Africa. Assuming that 1 million patients in Sub-Saharan Africa will receive treatment within three years, total requirements for international aid using this approach are projected to be $1.1 billion annually by year 3. In addition to the cost of antiretroviral therapy, UNAIDS has estimated that $3 billion per year is also needed for Sub-Saharan Africa for prevention, community support and treatment other than antiretroviral therapy[46].

If the AIDS treatment protocols prove successful, as we expect, up to three million people in Sub-Saharan African countries could become HAART recipients within a five-year time frame. By year 5 of the scaling up of this effort, therefore, we anticipate that donor assistance on the order of $3.3 billion would be needed for antiretroviral treatment for the region. These are ambitious targets, but they still would not cover large numbers of people in African that need care. Even more extensive coverage would likely require a significant expansion of basic health infrastructure into regions that now lack access to medical services. We have not calculated those additional infrastructure costs, but would add that they are investments that should be supported by the donor community in any event, not only for treating AIDS patients but for fighting a vast range of diseases that are currently claiming millions of lives in Sub-Saharan Africa.

Since Africa represents approximately 80 percent of the worldwide HIV-infected population that would require international donor support (low-income and/or high-prevalence countries), total global costs would be around 25 percent higher than the African costs. Thus, in three years, total cost projections of a global treatment effort would be around $1.4 billion and about $4.2 billion by year 5. India would represent about three-fourths of the non-African HIV-positive population requiring international grant support. We note that scaling up AIDS treatment must be

[43] GNP data are 1999 per the World Bank: http://www.worldbank.org/data/countrydata/countrydata.html.
[44] WHO. World health report. Geneva: WHO, 2000.
[45] Among middle-income countries (>$755 per capita GNP in 1999), prevalence is greater than 2 percent of adults in Botswana, South Africa, Thailand, Dominican Republic, and Guyana. These countries, like the low-income countries, will need grant support, with levels depending on the prevalence rate and national income.
[46] AIDS Epidemic Update: December 2000, www.unaids.org, page 20.

accompanied by scaling up tuberculosis treatment as well, especially since TB is the leading opportunistic infection related to AIDS in Africa.

Beyond the five-year horizon, the cost to the donor community will be subject to three forces. First, significant reductions in treatment costs are expected; this would be due not only to economies of scale and learning curves in drug production and delivery of medical services, but also to the introduction of new and increasingly effective treatment. Considerable research is also underway to produce an effective HIV vaccine, which if successfully developed could fundamentally reduce the costs of both prevention and treatment in later years. Second, the incidence of new infections is expected to peak and then decline. Increased treatment efforts presumably would correspond with scaled-up prevention efforts, which would result in decreased viral transmission, fewer AIDS cases, and ultimately, fewer candidates for HAART. Third, however, it is anticipated that initially the population of eligible patients will rise, especially as effective treatment protocols extend the lives of those currently suffering from AIDS. We cannot, at this point, make detailed cost estimates beyond a five-year horizon. We do believe, though, that the first two factors (declining treatment costs and a reduction in incidence) suggest that costs to the donor community will peak at several billion dollars per year, especially if treatment programs are complemented by intensive prevention programs, as recommended.

In order to broaden treatment access in a scientifically effective manner, we propose a coordinated global program. The international donor community, with significant U.S. participation, should provide financial and scientific support, while the recipient countries should commit to the needed political and scientific partnership. To achieve effective international coordination with appropriate scientific support, we propose a centralized funding and managerial structure at the international level, under World Health Organization (WHO) and UNAIDS leadership and with strong backing from international scientific institutions including the NIH and the CDC. Specifically, we recommend the following:

(a.) A single, global *HIV/AIDS Prevention and Treatment Trust Fund* should be established with joint WHO and UNAIDS leadership, and with strong support from international scientific institutions including the NIH and CDC. This trust fund would receive contributions from donor governments for AIDS treatment, prevention efforts, other related health care, and operational research in affected countries.

(b.) Project expenditures from the Trust Fund would be conditional on satisfying two principles:

  (i) All project proposals should originate in the recipient country by the government or a non-governmental organization backed by governmental support. This approach would ensure that the projects considered for funding are those for which there is confirmed political support and would avoid the pitfall where failed projects are blamed on a lack of political backing.

  (ii) All project proposals should undergo independent, expeditious review by a panel of experts external to the donors themselves and on accepted ethical, scientific, medical and public health principles. This process should be modeled on the "peer review" practices common in scientific funding agencies, but which are absent in international aid agencies. Expert review would ensure that only those

projects likely to have a measurable impact on health outcomes would qualify for donor funding. This principle is imperative to reassure taxpayers in wealthy governments that the international aid effort is deserving of support.[47]

7. How should the success or failure of this effort be evaluated?

The objective of our proposal is to provide HIV therapy for persons with symptomatic HIV infection in order to prolong life; reduce HIV transmission; reduce transmission of tuberculosis and other opportunistic infections; and stabilize decimated social structures in a context in which the efficacy of interventions can be monitored and objectively evaluated. A key component of this effort would be the rapid accumulation and dissemination of information, including health outcomes of trials, recommended treatment guidelines, and solutions to operational barriers in resource-poor settings. Moreover, disseminating this information would require a multilingual website to publish reports in a standard format and, in poor countries, continuing education and training for scientists and physicians who are routinely isolated from the global scientific community. We recommend the following:

(a.) All interventions should be carefully monitored to determine efficacy of treatment regimens, prevention of transmission, and emergence of drug resistance.
(b.) Outcome data must be rapidly and widely shared.
(c.) Guidelines for standards of care should be developed, disseminated, and revised on a regular basis.

Conclusion: It is time for a New Global Initiative to Provide AIDS Treatment in the Poorest Countries

As outlined at the beginning of this document, the leading objections to the widespread use of HAART in poor countries relate to infrastructure, patient adherence and drug resistance, cost, and political leadership. We believe this proposal systematically addresses each objection in a manner that can be assessed in both large pilot programs and clinical trials. In summary:

1. *Infrastructure*: Our proposal recommends the use of existing and developing infrastructures, such as networks that have been developed for directly observed therapy for the treatment of tuberculosis, and for maternal-to-child HIV transmission. The proposal also recognizes the immediate need to build additional infrastructure in resource-poor countries through the support of donor funding.

2. *Adherence/drug resistance:* The proposal recommends the use of simplified (once- or twice-daily) HAART regimens in addition to directly observed therapy and other strategies

[47] In the words of a former deputy administrator of USAID, "To ensure that the use of [aid] funds [is]…well informed from a scientific point of view, [aid agencies] should form a series of scientific advisory committees that would periodically review overall policies…as well as the allocation and use of [aid] funds." *Source*: C. Lancaster (2000). Transforming Foreign Aid. (Institute for International Economics: Washington), page 92.

designed to achieve high levels of adherence. These strategies have been associated with a high degree of treatment success and low levels of drug resistance in tuberculosis treatment, and treatment for both diseases should be integrated.[48]

3. *Cost:* At approximately $1,100 per patient per year, the total cost of treatment for 1–3 million HIV-infected individuals in Africa within 3-5 years would be easily managed by the world's wealthiest countries. Even at the five-year mark, the annual expenditure of about $3.3 billion would represent only about 0.01% of the aggregate GNP of these countries—or about one cent (1¢) of each $100 of income in these economies. Extending this program worldwide would add around 25 percent, so that the annual expenditure would total approximately $4.2 billion in the fifth year. This is a small price to pay for treatment on a meaningful scale in the midst of the worst worldwide pandemic in 600 years. It will likely save millions of lives, while leaving abundant capacity to fund AIDS prevention.

4. *Leadership:* The proposal recommends the establishment of an HIV/AIDS Prevention and Treatment Trust Fund, and calls on wealthy countries to provide financial and scientific leadership, and poor countries to provide necessary political and institutional support at both the national and community levels. Successful treatment delivery requires the full involvement of national governments and communities in the ultimate design and implementation of these interventions.

We conclude that a rapid scaling-up of scientifically monitored AIDS treatment in poor countries will prove feasible, affordable, and highly effective. There should be no further delay in launching a major international effort to save the lives of millions of HIV-infected persons. This effort will also help prevent the transmission of HIV infection to millions of healthy individuals in low-income and high-prevalence countries through the introduction of AIDS treatment.

[48] Martin S. Hirsch, et. al., "Antiretroviral Drug Resistance Testing in Adult HIV-1 Infection," Journal of the American Medical Association, May 10, 2000, Vol. 283, No. 18, 2417-2426.

ANNEX A

Estimating the Cost of Expanded AIDS Treatment in Africa

As the main text of the Consensus Statement makes clear, low-income countries (i.e., those having an annual per capita GNP < $755 annually on World Bank criteria) lack sufficient resources to finance AIDS treatment by themselves, even with discounts of 90% or more on drug costs.[49] A few somewhat wealthier developing countries (e.g., Botswana and South Africa) could finance limited AIDS treatment, but even then only a fraction of their needs. With the current supply of domestic resources, no country in sub-Saharan Africa can undertake widespread AIDS treatment; these countries are simply too poor relative to the prevalence and costs of the disease. This argument is often lost in popularized comparisons to Brazil, which has furnished free AIDS treatment to its citizens. Brazil's ability to provide treatment stems from the following: first, Brazil's average annual income is $4,400 (1999 estimates), and second, only 0.5% of adults there are HIV-positive. This is in stark contrast to Sub-Saharan Africa, where the average annual income is about $500 (1999 estimates) and the prevalence of adult infection about 9%, to say nothing of the most affected countries, where the infection rate can reach 40%.[50] [51]

The combination of low income and high HIV prevalence indicates that if AIDS treatment is supplied in Africa, international aid will have to pay for nearly all of it. Additional donor assistance also will be needed for countries where low income or high prevalence or both put resource needs for AIDS treatment beyond the financial capacity of the national government. Donated funds would finance both material requirements (e.g., medications, including antiretroviral drugs and drugs for opportunistic infections) and operational requirements (e.g., research and clinical operations) for AIDS treatment. We estimate that as of today, Africa would represent approximately 80 percent of the global needs for donor support and that remaining donor support would assist countries in South and Southeast Asia (e.g., India, where nearly 5 million people are infected with HIV) and in the Americas (e.g., Dominican Republic and Haiti).[52] Accordingly, this Annex focuses on the costs of AIDS treatment in Africa and recognizes that a global program would require approximately 25 percent more in overall donor financing than the Africa-specific program outlined here. We do not make cost estimates for the expansion of tuberculosis treatment that is needed in any event and that should accompany an expanded AIDS treatment effort, but endorse the additional funding of the global Stop TB campaign.

This costing model is based on a series of per-patient unit costs multiplied by the number of patients treated. We perform the analysis as static, taking into account only the need for treatment within the next 3 years. However, similar methods could be used to project future

[49] United Nations Conference on Trade and Development. Criteria for Identifying LDCs. Available at: http://www.unctad.org/en/subsites/ldcs/document/criteria.htm#B.
[50] T. Rosenberg. Look At Brazil. *New York Times Magazine* (January 28, 2001).
[51] UNAIDS. Report on the global HIV/AIDS epidemic. Geneva: UNAIDS, 2000.
[52] Among the universe of countries that are either low income (< $755 in 1999) or high prevalence (> 2% infection rate of adult population) or both, Sub-Saharan African countries include an estimated 25 million HIV-positive individuals, and the rest of the world another 5 million (including 3.2 million in India, 1.7 million in other parts of South and Southeast Asia, and 0.5 million in the Americas).

costs by using epidemiological projections of HIV prevalence, incidence, and future AIDS mortality to adjust the number of HIV-infected individuals needing treatment.

1. HIV testing costs

Prior to receiving treatment, each patient must test obtain counseling and test positive for HIV infection. Because the CDC and other agencies already have expended considerable effort on widespread HIV testing in Africa, we have estimated additional testing costs only for those most likely to benefit from immediate therapy. Determining HIV status is a non-recurring cost on an annual basis. The cost of an episode of counseling and testing has been estimated between $3 to $18, with the Harvard-Haiti project reporting a cost of $7. This is consistent with the assumptions of other published studies.[53] [54] Thus, we assume conservatively that each episode of counseling and testing costs $10 for those who test negative, and $20 for those whose test is repeated and who are confirmed positive. We estimate an HIV prevalence of 30% among those tested, when targeted to patients in hospitals and clinics. With an overall HIV prevalence of 10% in sub-Saharan Africa, it is likely that targeted testing will yield 30% of patients infected.[55] Of this 30%, we estimate that 1 in 3 will have advanced HIV disease and therefore require treatment. Thus, to achieve our goal of treatment for 1 million HIV-infected patients, approximately 10 million people will need to be tested. Of these 10 million individuals, three million will test positive for HIV, with 1 million candidates for treatment. The breakdown is as follows:

Initial screening tests

(10 million people) x ($10/person) = **$100 million (one time cost)**

Confirmation of HIV-positive status

(3million people) x ($10/person) = **$30 million (one time cost)**

It is important to note that counseling and testing expenses would be spread over several years. That said, the above testing effort would cost $130 million total, or $43 million annually if spread over three years. In addition to serving as a screening tool to select candidates for treatment, counseling and testing has the added benefit of informing those who are HIV-negative of their status, which has been shown to result in people changing their behavior to avoid future HIV infection.[56]

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[53] B. Varghese and T. Peterman. Test and Protect: HIV testing and counseling for HIV prevention in Africa. Presented at International AIDS Economic Network Symposium, Durban, South Africa, July 7-8 2000. Available at http://www.iaen.org/conferences/durbansym/papers/85Varghese.pdf.

[54] E. Marseille *et al.* (1999). Cost effectiveness of single-dose nevirapine regimen for mothers and babies to decrease vertical HIV-1 transmission in sub-Saharan Africa. *Lancet* 354:803-809.

[55] Since individuals with advanced AIDS disease will present themselves for testing at public clinics and other treatment sites, in order to join in treatment programs, the proportion of those tested that are HIV-positive will likely be much higher than the overall prevalence rate.

[56] Voluntary HIV-1 Counseling and Testing Efficacy Study Group (2000). Efficacy of voluntary HIV-1 counseling and testing in individuals and couples in Kenya, Tanzania and Trinidad: a randomized trial. *Lancet* 356:103-112.

2. Drug costs:

For most patients (70%), we assume an annual drug cost of $500 per patient per year for HAART (see main text). For the remaining 30% of patients, we assume a more expensive regimen is necessary at increased costs of $1,000 per patient per year. This assumption is based on data that show that patients who develop virologic resistance to an initial regimen typically require more or different drugs in a "salvage" regimen as well as other treatment strategies for late-stage AIDS. This yields a probability-weighted, per patient drug cost of $650/year across the board.

For symptomatic AIDS treatment, such as demonstrated by the Harvard group in Haiti (see main text), we assume that only patients with advanced HIV disease satisfy the criteria to begin treatment. Furthermore, because the time from AIDS onset to death is typically under one year in Africa,[57] [58] we estimate that the number of patients who would begin therapy in Africa is roughly equal to the number of AIDS deaths reported by UNAIDS in 2000. Therefore, approximately 2.4 million people in Africa are anticipated to be candidates for initial treatment.[59] We calculate the drug costs for treating 1 million patients as follows:

(1million people) x ($650/patient-year) = **$650 million/year**

It is important to note that this approach may underestimate the number of candidates for treatment, because it is retrospective by one year in a growing epidemic and because the number of AIDS deaths is an imperfect proxy for the number of people living with advanced AIDS. In addition, three factors may further limit the number of patients who receive initial treatment: (1) Not every AIDS patient will be interested in, willing, or able to be treated; (2) Many AIDS patients are beyond the reach of the governmental or non-governmental health systems, either as they exist now or as they might exist in the next 3-5 years, and; (3) Not all countries presently have the top-level political commitment to commence widespread AIDS testing and treatment. *Despite these limitations, we consider it ambitious but possible for 1 million people to receive HIV/AIDS treatment within 3 years.* This would likely be less than one third of late-stage AIDS patients in Africa, but over a one hundred-fold increase in the number of such patients receiving HAART today.

We calculate the drug cost for treating 1 million patients as:

DRUG: (1million people) x ($650/patient-year) = **$650 million/year**

3. Directly observed therapy (DOT) costs:

[57] D. Morgan, et al. (2000). Survival by AIDS defining condition in rural Uganda. *Sex Transm Infect* 76: 193-7.
[58] D. Morgan et al. (1997). HIV-1 disease progression and AIDS-defining disorders in rural Uganda. *Lancet* 350: 245-50.
[59] UNAIDS (2000). AIDS Epidemic Update: December 2000. Available at http://www.unaids.org/wac/2000/wad00/files/WAD_epidemic_report.PDF.

If the drugs are administered through directly observed therapy, additional costs will accrue. For DOT in Haiti, an *accompagnateur* (i.e., a treatment observer) is typically paid $100/month to supervise the medication of 6 patients. This would be an appropriate wage level in most of Africa and would keep turnover of treatment observers low. Assuming capital expenditures are negligible, the average cost per patient is therefore $200/year. Total annual costs for DOT are as follows:

DOT: (1million people) x ($200/patient-year) = **$200 million/year**

4. Clinical costs

For those who test HIV-positive and begin HAART, approximately 6 clinic visits annually are likely to be needed to effectively monitor the therapeutic response to and toxicity from antiretroviral drugs. Each clinic visit would require consultation with a physician, nurse, or other health worker, and, if available, a panel of relatively inexpensive blood tests. These tests would not include more expensive CD4 cellcounts and HIV viral load testing, as these would be performed regularly only on those patients in clinical trials, in order to determine the contribution of such tests to outcomes. Unit costs for an outpatient consultation are very low in impoverished regions with poor health infrastructure (sub-Saharan Africa, $3) and slightly higher in middle income countries with a more established health infrastructure (Thailand, $14).[60] Taking the latter figure, plus an allowance for the blood tests and opportunistic infection prophylaxis, we estimate that the total cost of each clinic visit would not exceed $25 per visit, or $150 annually. While the costs of laboratory tests, such as CD4 cell count and HIV viral load, in the developing world are not well-defined, costs for a single CD4 cell count and HIV viral load test are an estimated $80 per person per year to define treatment failure. We estimate the clinical costs of ongoing treatment for 1 million patients as follows:

CLINICAL: (1million people) x ($230/patient-year) = **$230 million/year**

5. *Clinical research*

In keeping with the view that a scaling-up of AIDS treatment must be accompanied by clinical research in order to determine optimal treatment strategies in poor countries, additional costs will be associated with the enrolling and monitoring of patients in different trials. These costs will vary greatly depending on the scientific question posed by the trial and the laboratory or clinical work necessary for data collection. We conservatively estimate that most trials can be supported for under $500 per patient per year, an amount sufficient to enroll and follow each patient in the trial and to perform periodic CD4 cell count or HIV viral load testing, at a remote facility if necessary. In the United States, nearly 1 million people have been treated for AIDS, with about 100,000 of those (10%) enrolled in clinical trials. through the AIDS Clinical Trials Group, the CPCRA, HIVNET, the VA system, and other research groups. Based on these numbers, we estimate that in the first several years about 50,000 people in resource-poor countries would participate in trials. Our calculations are as follows:

[60] See Table 4.1 in World Bank (1997). Confronting AIDS (Oxford University Press, New York).

RESEARCH: (50,000 people) x ($500/patient-year) = **$25 million/year**

6. Total

Summing these costs, we estimate the following total:

TESTING:	Annualized cost based on 3-year cycle (see above)	**= $43 million/year**
DRUG:	(1million people) x ($650/patient-year)	= **$650 million/year**
DOT:	(1million people) x ($200/patient-year)	= **$200 million/year**
CLINICAL:	(1million people) x ($150/patient-year)	= **$230 million/year**
RESEARCH:	(50,000 people) x ($500/patient-year)	= **$25 million/year**

TOTAL = $1.123 billion/year

We conclude that that the total cost of treatment, comprising the above expenditures, would be approximately $1,123/patient-year, or slightly over $1.1 billion annually for the 1 million patients that we believe can be treated in Africa within the next 3 years. This number would increase in later years, as treatment could be expanded to a larger number of patients. **By year 5 the aim would be to increase coverage to 3 million individuals or more**. This would require approximately $3.3 billion annually, a sum that is small in proportion (0.01% of an aggregate GNP of nearly $23 trillion) to the wealth of the donor countries called on to fund this effort.[61]

Our estimate of $1,123 per patient per year is consistent with other studies which show non-drug costs of delivering HAART in the range of several hundred dollars, or roughly on par with the discounted price of antiretroviral drugs themselves. For example, researchers in Brazil have reported the non-drug HAART costs of about $350/patient-year for that government's national treatment program.[62] World Bank estimates, at over $800/patient-year, are somewhat higher.[63] Both these estimates include advanced diagnostics such as CD4 or viral load testing; however, they do not make provision for directly observed therapy in order to maximize patient adherence and forestall drug resistance, nor do they include the cost of clinical research in order to collect data and therefore optimize AIDS treatment in poor countries.

We believe that an immediate effort to treat 1 million AIDS patients in poor countries, as described in this document, can take place with a limited amount of investment in new infrastructure, the cost of which is implicit in the figures we present. However, as treatment is

[61] The high-income countries had a combined GNP of $22.921 billion in 1999, according to the World Bank Development Report 2000/2001.

[62] D. Cyrillo, L. Paulani, B. Aguirre. Direct Costs of AIDS Treatments in Brazil: A methodological comparison. Presented at International AIDS Economic Network Symposium, Durban, South Africa, July 7-8 2000. Available at http://www.iaen.org/conferences/durbansym/papers/13cyrillo.pdf.

[63] World Bank AIDS Campaign Team for Africa (2000). Costs of Scaling HIV Program Activities to a National Level in Sub-Saharan Africa: Methods and Estimates.

expanded to a larger number of patients in increasingly remote areas, infrastructure will become limiting unless there are additional outlays for training medical personnel and capital expenditures for physical infrastructure. Such additional outlays would have multiple benefits beyond HIV/AIDS treatment, as they would support a more general expansion of health services in Sub-Saharan Africa. We do not estimate those additional outlays here.

Cost-Effectiveness Considerations

The above discussion focuses on the costs of AIDS treatment, without considering the benefits or the "effectiveness" of treatment. Cost-effectiveness analysis considers both factors, specifically the total cost of an intervention and its corresponding clinical effectiveness in order to understand the value of treatment. These two outcomes are compared as a ratio, or cost per unit of life expectancy. More advanced cost-effectiveness analyses compare two or more interventions; the ratio is calculated as the incremental change in total costs, divided by the incremental change in life expectancy, compared to another intervention. In this scenario, the clinical benefit (or life expectancy) is measured in years of life saved.

There is no question that HAART therapy is cost effective in rich countires, compared not only to other HIV interventions but also to interventions for a variety of diseases and conditions.[64] Because HAART keeps people alive and generally in good health, each year of effective treatment for those with advanced HIV disease (those who would otherwise die) generally leads to an additional year of life saved. In fact, the cost-effectiveness of AIDS treatment roughly corresponds to its actual cost. In sub-Saharan Africa, then, where HIV/AIDS treatment is predicted to cost approximately $1,123/patient-year, its cost-effectiveness ratio, the cost per unit of clinical benefit, will be approximately the same.

It is important to note that this number is a preliminary estimate, since it is not based on a detailed African model of HIV disease progression both with and without HAART. Moreover, it does not incorporate the savings that HAART will permit in regard to hospital stays and treatment for opportunistic infections, as has been the experience in the United States, other wealthy countries, and middle-tier developing countries such as Brazil.[65] [66] Nor does this cost estimate include HAART's epidemiological benefits, which have been shown to reduce overall disease incidence both by reducing the HIV viral load and transmissibility of HIV-positive individuals and by improving the efficacy of prevention programs (see main text). Finally, this estimate does not consider the enormous economic and social gains that will be achieved by saving the lives of parents, and thereby reducing the number of children that are orphaned by AIDS.

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[64] K. Freedberg *et al.*(2001). The Cost Effectiveness of Combination Antiretroviral Therapy for HIV Disease. *NEJM* 344:824-831.

66. S. Bozzette *et. al.* (2001). Expenditures for the Care of HIV-Infected Patients in the Era of Highly Active Antiretroviral Therapy, *New England Journal of Medicine* 344:817-823

[66] "Antiretroviral Therapy: Brazil's Experience," mimeo, Ministry of Health, National STD/AIDS Programme, 2000.

Given the societal-wide ramifications of AIDS discussed in the text, and the ethical and practical considerations facing the donor world, we believe that expenditures of approximately $1100 per year of life saved should be fully acceptable to the international community. We note, in addition, that such expenditure in Africa would also be justified according to conventional criteria used in the cost-effectiveness literature. According to theoretical studies, and to the practice in the American public health literature, the economic value of a life-year saved is commonly estimated to be 2 to 3 times the average annual U.S. income, and sometimes higher.[67] On this basis, medical interventions that save a life-year at a cost of 2 to 3 times the average income (i.e., an intervention cost of $70,000 to $105,000, given the average U.S. income of $35,000) are often deemed to be acceptable investments in American public health. Recent studies show that HAART in the United States has a cost-effectiveness ratio of about $15,000 per year of life saved, and thus provides excellent value on the cost-effectiveness spectrum.[68] Given the lower treatment costs in Africa, HAART in Africa is likely to be about fifteen times more cost-effective than HAART in the United States, and fifty or more times as cost-effective as many other routinely accepted medical therapies in the United States.

In the African context, where average annual income is around $500 per year, and even higher for AIDS patients at the prime of their working lives, a medical intervention of $1,100 per life-year saved would also fall within the conventional bounds of 2 to 3 times average annual income. This is even more clearly the case in countries with higher per capita incomes. Finally, this type of intervention will be even more cost-effective when one considers the decrease in the spread of HIV infection and other social savings that could be achieved by treating large numbers of patients.

Conclusions

We have outlined the likely cost and cost-effectiveness implications of a major effort to bring AIDS treatment to Sub-Saharan African countries. In order to provide treatment for 1 million HIV-infected individuals, we estimate costs of about $1.1 billion annually. This cost may be trebled, to about $3.3 billion, within five years in order to treat 3 million people with AIDS. The cost of a global program that includes not only Africa but also the low-income and/or high-prevalence countries in other parts of the world would add approximately 25 percent to this cost, bringing the total donor needs to around $1.4 billion annually during the first three years, and around $4.2 billion annually by the fifth year. While the cost of these therapies remains far beyond the reach of African and other poor countries, the modest overall costs to high-income countries with large-scale treatment and prevention programs, and their potential contribution to prevention of future HIV transmission should be persuasive to the international community. It is increasingly clear that immediate, widespread AIDS treatment will be an extremely sound global

[67] See C. Phelps and A. Garber (1997). "Economic Foundations of Cost Effectiveness Analysis," *Journal of Health Economics* 16:1-31. Their own analysis comes up with a figure of around two times annual median income as the threshold cutoff point (p. 25), a criterion that varies with the age of the patient. An intervention like HAART that applies heavily to workers in the prime years of working life would tend to have higher threshold levels for cost-effectiveness. Moreover, these authors cite other works and conventional criteria that put the threshold at much higher than two times annual income.

[68] K. Freedberg *et al.*(2001). The Cost Effectiveness of Combination Antiretroviral Therapy for HIV Disease. *NEJM* 344:824-831.

investment in the economic, social, and political wellbeing of the world's resource-poor countries, those that have been hardest hit by the scourge of AIDS.

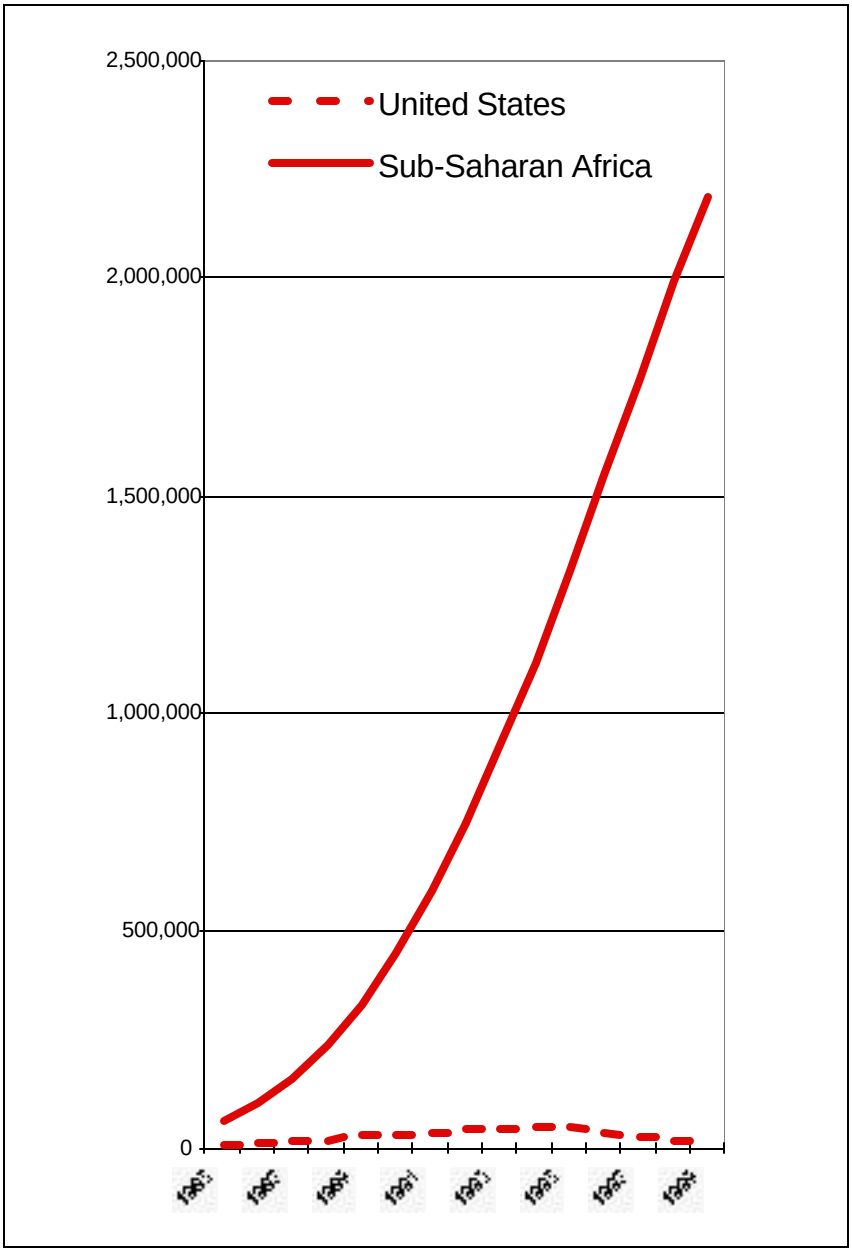

Figure 1: Trends in age-adjusted AIDS death rates, 1985-1999. Shown are annual AIDS deaths for sub-Saharan Africa (solid line) and the United States (dashed line). In the U.S., HAART was introduced in 1995, accounting for the visible decline in deaths. Sub-Saharan Africa, with apparently more virulent subtypes of HIV and ineffective health systems, has experienced a constant increase without the diminution in deaths that HAART might allow. *Source:* UNAIDS.

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