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Topics in HIV Medicine™

A publication of the International AIDS Society–USA

Highlights of the 8th Conference on Retroviruses and Opportunistic Infections, Part 2

Perspectives

Special Contributions

About This Issue

Our June issue contains 2 special contributions. The first is an update of International AIDS Society–USA figures illustrating antiretroviral drug resistance mutations, previously published in May, 2000, in the *Journal of the American Medical Association*. Members of an International AIDS Society–USA Resistance Mutations Project Panel have revised the figures to incorporate new data in the field. The second special contribution is a consensus statement on the provision and use of antiretroviral therapy in poor countries. Authored by a multidisciplinary group of 141 members of the Harvard University faculty, the statement offers a detailed argument for the wealthy countries of the world to fund antiretroviral treatment in the developing world.

In a related article, we provide an edited transcript of a lecture by Jeffrey D. Sachs, PhD, at the opening session of the 8th Conference on Retroviruses and Opportunistic Infections in February, "From Talk to Action in Fighting AIDS in Developing Countries." Also included is a summary of research presented at the Retrovirus Conference on HIV pathogenesis and vaccine candidates, by Bruce D. Walker, MD; and 2 summaries of talks given at recent International AIDS Society–USA courses. The first, by Paul E. Klotman, MD, covers new research on HIV-associated nephropathy, and the other, by Felix F. Carpio, MD, MPH, discusses HIV disease management in Latino populations. Summaries of additional lectures given at the International AIDS Society–USA annual winter/spring course series will appear in future issues.

Of note, complimentary subscriptions to *Topics in* HIV *Medicine* are currently provided to about 12,000 HIV practitioners in the United States and almost 500 practitioners living in foreign countries, including the developing world. We are working to increase the number of subscriptions in developing countries, and to secure funding for the production and postage costs required. Readers interested in making a tax-deductible donation toward distribution in developing countries should contact the International AIDS Society–USA at the address listed below.

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Correspondence
Topics in HIV *Medicine* welcomes editorial correspondence. Address letters to:

Editor, *Topics in* HIV *Medicine*
International AIDS Society–USA
Presidio of San Francisco
1001 B O'Reilly Avenue, PO Box 29916
San Francisco, CA 94129-0916

Phone: (415) 561-6720
Fax: (415) 561-6740

Web site: http://www.iasusa.org
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HIV Pathogenesis and Prospects for Vaccine Development

Bruce D. Walker, MD

As the HIV pandemic continues to gather force, there is a widening gap in access to care in developed and developing countries. The persistence of this sobering reality was highlighted in major presentations on the opening and closing days of the 8th Conference on Retroviruses and Opportunistic Infections in Chicago. An effective vaccine might one day lessen this discordance, and data presented on vaccine trials in animals give reason to be optimistic. In addition, unraveling the factors that contribute to the typically relentless progression of HIV infection may in the end not only aid in the development of effective vaccines, but may also help to stem the progression of disease. This review summarizes important progress made in understanding HIV pathogenesis and discusses these advances in the context of exciting new data presented in the realm of candidate HIV vaccines.

Acute Infection

Accumulating data suggesting that early events in acute HIV infection may influence the ultimate progression of disease necessitate a better understanding of the initial events following exposure to virus. Studies over the past 2 years have shown that T helper cell responses to HIV are diminished or absent in persons with progressive chronic HIV infection, and additional studies at this Conference underscore this defect (Abstracts 154, 156, 158, and 160). The reasons for this lack of T helper cell responses have been unclear, but a study in macaques supports the notion that early immune damage is occurring, in that active memory cells appear to be the primary target for simian immunodeficiency virus (SIV) in acute infection (Veazey et al, Abstract 506). By analogy, one would expect to see something similar in acute HIV infection, and such studies are clearly warranted.

Dr Walker is Professor of Medicine at Harvard Medical School and Director of the Partners AIDS Research Center in Boston, Massachusetts.

Since most acute infections worldwide occur across a mucosal barrier, dendritic cells (DCs) in the lamina propria have long been thought to play an important role. The potential role of a recently described surface molecule preferentially expressed on DCs was reviewed in a State-of-the-Art Lecture by van Kooyk (Abstract L10). Termed DC-SIGN for DC-specific, ICAM-3-grabbing non-integrin, this molecule is thought to mediate DC trafficking and T cell binding. It is a type II mannose-binding C-type lectin that recognizes carbohydrates and serves as the major HIV receptor on DCs through a specific interaction with gp120. It does not mediate virus entry, so it is distinct from CD4 and CCR5. Instead, it enhances infection of activated T cells. It can stabilize HIV-1 for more than 4 days, because binding to DC-SIGN protects HIV from proteases that are present in plasma. This then likely allows for transport of the virus to regional lymph nodes, where infection can be propagated further. Whether targeting of DC-SIGN with specific therapies would have an antiviral effect remains to be determined, but is becoming an active area of investigation.

Other factors potentially influencing transmission and subsequent progression were also suggested in a variety of studies. At the time of acute infection plasma viremia is quite high—one study showed an average of over 10 million viral particles per milliliter of plasma when acute patients were first evaluated (Walker, State-of-the-Art Lecture, Session 37). At these early times prospects for transmission are high. One study indicated that sexual transmission may actually precede the symptoms of acute infection (Pilcher et al, Abstract 411). The investigators examined 5 cases in which sexual transmission occurred during acute HIV infection in the source patient. Their findings suggest that transmission can occur up to 2 days before the onset of symptoms, and the finding of clusters of cases transmitted by persons with acute infection provides even more impetus for the early identification of these individuals. Another study suggested that preseroconversion levels of T cell receptor rearrangement excision circles (TRECs) may influence disease progression, with low TREC content associated with more rapid disease progression (Zhang et al, Abstract 373). The potential mechanisms involved remain to be defined.

One study of acute infection is worthy of special mention. Rizzardi and coworkers (Abstract 759) treated persons with acute HIV infection with 8 weeks of the immunosuppressive agent cyclosporin A (CSA) and then followed them longitudinally. Comparison was made to persons treated with highly active antiretroviral therapy (HAART) alone. This therapy rapidly and effectively increased CD4+ cell counts, and HIV-specific CD8 immune responses were maintained. One potential explanation for this finding would be that virus is less able to infect the CSA-treated cells since this compound has an antiproliferative effect. Further studies will be needed to determine the effects of this intervention on long-term outcome, including the ability to use supervised treatment interruption (STI) with the intention of gaining immune control of infection.

This report is part of *Topics in HIV Medicine's* highlights of the 8th Conference on Retroviruses and Opportunistic Infections, held in February, 2001. In this article Dr Walker summarizes the new data on HIV pathogenesis and vaccine development presented at the Conference.

Persistence of Viral Reservoirs

Lifelong therapy will almost certainly be required to treat HIV disease, since viral eradication is not likely to occur. This sobering point was further emphasized in a State-of-the-Art Lecture from Siliciano (Abstract L5), who showed essentially no decay in the latent viral reservoir in persons highly adherent to their medication regimens. With follow-up now out to 4 or 5 years in these individuals, there has still been no change in reservoir size compared to initial values. In fact, his studies suggest that the survival of latently infected cells is

the same as their uninfected counterparts. Maintenance of viral species in the reservoir is very persistent, such that resistance mutations can be deposited in this reservoir and will likely persist for the life of the individual. The persistence of drug-resistant mutations that enter this reservoir was further demonstrated in persons undergoing STIs (Deeks et al, Abstract 292; Hance et al, Abstract 293). Even though the half-life of infected cells in the reservoir may be shortened on more intensive regimens (Ho et al, Abstract S17; Ramratnam et al, Abstract 502), and decay rates of cell-associated infectivity may be more rapid in persons treated earlier after acute infection (Wong et al, Abstract 503), such regimens are not practical and the likelihood of eradication does not appear to be increased.

Another issue that is still to be adequately addressed is the possible presence of other reservoirs. At this meeting, the kidney was revealed as a potential haven for HIV. Virus was identified in mesangial cells in persons who have HIV-related nephropathy (Marras et al, Abstract LB3). The possibility that this represents a separate sanctuary was suggested by the finding of divergent evolution of viruses obtained from kidney and peripheral blood. Another possible reservoir is the macrophage, but studies presented indicated that the decline of virus in macrophages very closely paralleled the decline in CD4+ cells, suggesting against this as a proposed mechanism of the slower second-phase decline in plasma viremia (Bucy et al, Abstract 507). Instead, these data were interpreted to suggest that the slow decline after the first week might be due to slow release from tissue sanctuary sites yet to be defined. The brain is one potential site, an argument supported by data showing divergent evolution of viruses obtained from cerebrospinal fluid compared to blood and other tissues (Ellis, Abstract S19).

A number of studies addressed viral dynamics, and highlighted controversies still have not been fully rectified. Using deuterated glucose to label the DNA of proliferating cells, 4 normal subjects and 7 controls were examined by Mohri and colleagues (Abstract 269). Lymphocyte turnover rates were accelerated by several-fold in HIV infection compared with uninfected controls, and this was true for both CD4+ and CD8+ cells. With institution of HAART, these turnover rates rapidly decline and reach near normal levels by 1 year. These results were interpreted to mean that the low CD4+ cell count in AIDS is a consequence of increased cell death rather than decreased cellular regeneration. However, other studies presented suggest that increased cell turnover and decreased thymic output both contribute to the inability to maintain normal cell numbers (Douek et al, Abstract 270).

Immune Responses to HIV

The role of the immune system in controlling HIV replication was further defined through a number of presentations at this meeting. In particular, exciting data presented provide evidence that may facilitate eventual induction of effective neutralizing antibody responses. Desrosiers in the Bernard Fields Memorial Lecture (Abstract L1) presented data from studies of the role of envelope glycoprotein in avoidance of antibody-mediated recognition. Using SIV and simian-human immunodeficiency virus (SHIV) model systems to study mutations in the V1-V2 region that affect carbohydrate attachment of gp120, he demonstrated that removal of carbohydrates can enhance neutralization sensitivity and that antibodies elicited by such mutant viruses can confer augmented immune control following subsequent pathogenic viral challenge, as evidenced by a lower viral set point. Although there were few additional studies of neutralizing antibodies at the meeting, this lecture alone served to fuel enthusiasm that effective neutralizing antibody induction might still be a reality.

In contrast to the paucity of presentations related to humoral immune responses, numerous presentations addressed the role of cellular immune responses in control of viremia and pathogenesis of infection. The breadth of the cytotoxic T lymphocyte (CTL) response was shown to extend beyond the traditionally studied epitopes in Gag, reverse transcriptase, Env, and Nef. Using new techniques to quantitate interferon gamma (IFN-γ) release by CD8+ cells as a measure of CTL activity, it was demonstrated that significant responses can be detected to Tat and Rev (Addo et al, Abstract 167), as well as the accessory proteins Vif, Vpr, and Vpu (Altfeld et al, Abstract 168). These techniques have also allowed for the comprehensive assessment of responses to all of the expressed proteins of HIV, showing that 18 of 18 persons studied over a wide range of viral loads and CD4+ cell counts had detectable responses (Betts et al, Abstract 272). However, in contrast to previous published reports of a correlation between viral load and CTL magnitude when A2 restricted responses alone are studied, these more comprehensive studies failed to show any significant correlation. Other studies examined CTL epitope density in different regions of the virus, including p17 and Nef, and identified a clear correlation between predicted proteasomal cleavage sites and actual epitope boundaries (Yusim et al, Abstract 271). Such studies begin to address the issue of relative immunodominance of CTL responses, an issue of critical relevance to vaccine design.

CD8+ cells have been shown to lyse infected cells but also to release soluble inhibitory factors that include beta chemokines that inhibit R5 viruses as well as other factor(s) that inhibit X4 viruses. The precise characterization of the elusive X4 inhibitory factor(s) remains to be determined. There was relatively little presented at the meeting relating to this response. Persons who are treated in the acute stage of infection appear to develop particularly robust CD8+ cell noncytotoxic activity, and the ability of this response to inhibit viral replication appears to be best when there is direct cell-to-cell contact (Chun et al, Abstract 504). However, full characterization of the factor remains elusive.

In the past 2 years numerous publications have indicated a role for virus-specific CD4+ T helper cells in effective control of chronic HIV infection, and additional data at this meeting further support this notion, although not without persisting controversies.

The relationship between CD4+ T helper cells and CTLs was further evidenced by a macaque immunization model, in which induction of CTLs was associated with the induction of strong CD4+ T helper cells directed against the virus (Belyakov, Abstract S5). Such relationships were also implied in studies of natural infection in humans (Imami et al, Abstract 158; Autran et al, Abstract 160). The delineation of this relationship between CD4+ T helper cell responses and CTL function should be important, since it will help to guide immunotherapeutic interventions for persons who are already infected.

A number of studies addressed the important issue of what factors contribute to the lack of immune control in chronic infection. Insights into the lack of T helper cell responses to HIV in persons with chronic infection were provided by studies using proliferation assays, IFN-γ and interleukin 2 (IL-2) ELISPOT assays, and major

histocompatibility complex (MHC) class II tetramers. Subjects studied included those undergoing STIs. Virus-specific T helper cells were found to persist during periods of viremia, but to be incapable of proliferation (McNeil et al, Abstract 156). A second study also found that defects in proliferation may be independent of the ability to secrete IFN-γ (Pires et al, Abstract 157). The demonstration of HIV-specific class II tetramers that allow for direct staining of the antigen-specific cells should help to further resolve these issues (Yassine Diab et al, Abstract 155). Assessment of reasons for immune failure of CTL responses included the potential inability of HAART to restore DC number and function (Donaghy et al, Abstract 40) and lack of effective maturation of CTLs into fully functional effector cells (Champagne et al, Abstract 274; Van Baarle et al, Abstract 275; Papagno et al, Abstract 276). The demonstration of skewed maturation of CTLs in HIV infection compared to cytomegalovirus infection in the same individuals suggests that there are specific factors that impair differentiation selectively, such as perhaps a lack of sufficient HIV-specific T helper cell function (Abstracts 274 and 275).

Progress in Vaccine Studies

The opening and closing sessions of this Conference were marked by lectures describing in vivid detail the desperate global situation with respect to the HIV pandemic, which continues to gather force. The need for a vaccine has never been greater, and important progress toward this goal was presented at the Conference. This included not only the aforementioned success with induction of neutralizing antibodies (Desrosiers, Abstract L1), but also a number of other animal models in which protection from disease was a common theme.

One of a number of impressive immunization studies was presented by Robinson and colleagues (Abstract 24). This group had previously demonstrated that DNA immunization followed by boosting with a modified vaccinia virus Ankara (MVA) vector resulted in induction of strong immune responses, and here presented the results of challenge studies. Following the MVA boost, impressive levels of CD8 responses were obtained—up to 18% of CD8+ cells by tetramer analysis. This study design was impressive because the investigators waited 6 months after the final booster immunization until they challenged with a pathogenic virus. This meant that the immune responses were in memory at the time of encounter with virus. All animals became infected upon challenge, but all vaccinated animals had preservation of CD4+ cell number and most animals were able to control viremia at levels below 1000 copies/mL plasma. All 24 vaccinated animals remained clinically healthy, with vigorous virus-specific cellular immune responses and absence of detectable virus in lymph nodes by in situ hybridization. Clinical trials in humans are slated for later this year.

Other impressive studies also showed that although complete protection from viral challenge could not be obtained, viral set point could be dramatically influenced. One approach involved the use of phage-displayed peptides, in which 4 of 5 challenged animals maintained low viral loads despite becoming infected (Chen et al, Abstract 26). Another involved the use of vesicular stomatitis virus recombinant vectors (Rose et al, Abstract 23). Although follow-up is brief in these animals, the early data indicate a 100-fold or greater decrease in viral load in the vaccinees compared to controls. New delivery methods for a variety of candidate vaccines (Otten et al, Abstract 27; Marovich et al, Abstract 29) and development of polyvalent constructs (Cho et al, Abstract 28) may enhance the ability to achieve broader and more durable vaccine-induced immune responses. In addition, some of these approaches are being adapted for use as therapeutic vaccines, an approach for which there is presently considerable enthusiasm and yet few firm data.

Most studies of vaccines have examined immune responses in peripheral blood, but induction of mucosal immune responses may be particularly relevant to the development of an effective vaccine. Belyakov and colleagues (Abstract S5) presented data in a murine model of virus infection, in which mice are immunized with a peptide-based vaccine and then challenged with a vaccinia virus expressing HIV proteins. Intrarectal immunization resulted in induction of CTLs in Peyer's patches and intestinal lamina propria, and in CD8+ T cell-mediated protection, whereas subcutaneously immunized animals developed CTLs in the spleen and not the gut, and were not protected. Extension to a macaque model confirmed the advantage to intrarectal immunization when the animals were challenged with a pathogenic SHIV, in that the intrarectally immunized monkeys had more effective clearance of plasma viremia and greater preservation of CD4+ cell counts despite infection. Studies examining mucosal T cell responses in humans should facilitate assessment of candidate vaccines (McElrath, Abstract S6).

Although the animal trial data presented are impressive, human data are most eagerly awaited. Promising candidates include alphavirus vectors (Johnston, Abstract S7) and a polyepitope vaccine (Hanke, Abstract S8), both of which are slated to be in larger human clinical trials in the near future. The initial phase of testing of the polyepitope vaccine, presented in the context of a DNA and MVA vector, is already in phase 1 trials in humans. The vectors mentioned in the animal trials above are also all on paths toward clinical development, and initial data from some of these can be anticipated at the Retrovirus Conference in 2002.

Immune Augmentation in HIV Infection

The demonstration that some persons are able to coexist with the virus for 20 years or longer without developing disease has sparked intense interest in the mechanisms by which virus is held in check. As indicated above, compelling evidence now exists for immune-mediated control of virus in these individuals. Three additional factors have fueled interest in immune reconstitution as a therapeutic intervention: (1) the demonstration that HAART leads to increases in naive cells, (2) the demonstration that early treatment of acute infection leads to augmented T helper cell responses, and (3) anecdotal reports that treatment interruption after treated acute infection has been associated with long-term control of viremia. Together, these factors have fostered a new area of investigation, which is controversial enough already that it merited its own session at the Conference. This is variably termed "supervised treatment interruption" or "structured treatment interruption."

It is important in any discussion of STI to discuss the settings in which it is being applied, since the objectives in these settings may be very different. Table 1 lists the 3 different objectives to STI that have been discussed. This review will deal with all 3, but will focus in particular on the use of STI to enhance immune responses, since this is the approach that has been most extensively tested thus far.

Data were presented in which STI was used with the objective of boosting immune function in both acute and chronic infection. This distinction appears to be important in assessing the results of the studies presented, since the results thus far in acute infection appear more impressive. In addition, one must be aware that there is no accepted definition for acute cohorts, and they are actually quite different among different studies. One acute study presented involved subjects with an average plasma viral load of 10 million HIV RNA copies/mL at the time of enrollment (Walker, State-of-the-Art Lecture, Session 37), whereas another examined persons with an average viral load of less than 100,000 HIV RNA copies/mL (Markowitz et al, Abstract 288). One must also make a distinction between treatment cessation and treatment interruption in order to ensure objective comparisons.

The effects of STI in acute infection indicate that at least transient control of viremia may be possible with this approach (Walker, State-of-the-Art Lecture, Session 37). In follow-up of the first 8 persons to undergo repeated cycles of therapy interruption, a total of 14 subjects were presented. Treatment was interrupted after at least 8 months of successful therapy, and reinstituted for a viral load persistently above 5000 copies/mL (for greater than 3 weeks) or a single viral load of greater than 50,000 copies/mL. Of the first 14 subjects, 4 were able to persistently control viremia after a simple treatment cessation, 2 were able to persistently control after a second treatment interruption, and 1 was reported to maintain viral load at less than 5000 copies/mL after a third interruption. The longest follow-up is now over 400 days, with some persons able to maintain viral loads of less than 500 copies/mL. Of the 14 subjects, 7 remain off therapy and are considered successes, and 6 are still involved in the second, third, or fourth STI and cannot yet be evaluated. There is only 1 person who underwent 4 STIs in whom viremia was not controlled, and treatment would be considered a failure. However, this person has a viral load of 7445 copies/mL after 128 days off therapy for the fourth time, and has chosen not to resume therapy because of the recent changes in the treatment guidelines.

Another trial of immune control following treatment of acute infection was one in which persons decided on their own to discontinue medications, and is therefore a treatment termination study. These individuals, some of whom had received therapeutic immunizations while on HAART, had lower initial viral loads (less than 100,000 copies/mL) at the time they were diagnosed with acute infection. After a mean of 258 days off therapy, viral loads range from 2.9 to 4.2 $\log_{10}$ copies/mL in those remaining off therapy. Two persons have maintained viral loads of less than 1000 copies/mL, but 7 of 14 have resumed HAART. There was no evidence that the immunization had a beneficial effect. Thus treatment termination, particularly in early as opposed to acute infection, does not appear to confer as clear an effect on set point viral load.

The results, both anecdotal and published, of successful control of viremia following treatment of acute infection have fueled additional studies in chronic infection. The largest trial to date is the Swiss-Spanish Intermittent Treatment Trial, presented by Fagard and colleagues (Abstract 357). This trial included 128 subjects, who were successfully treated with HAART and then underwent 4 cycles of 2 weeks off therapy and then 8 weeks on therapy. At 40 weeks into the trial medications were discontinued until viral load rose above 5000 copies/mL. Twelve weeks after stopping therapy, only 9 of 54 subjects who could be evaluated had an HIV RNA level below 5000 copies/mL, and those who did remain off therapy were more likely to have initiated therapy early after diagnosis of acute infection. In the end the strategy appears to have worked for about 1 in 6 subjects, and again durability is not yet known, nor is it clear how much this is different from what would be expected without any intervention. In another trial of STI in chronic infection (García et al, Abstract 289), baseline viral load decreased an average of 0.54 $\log_{10}$ copies/mL in the STI group, whereas the control group experienced an increase of 0.24 $\log_{10}$ copies/mL over the same time. The mean HIV RNA load in the STI group was approximately 10,000 copies/mL, compared to 50,000 copies/mL in the controls. Both higher HIV-specific T helper cell responses and higher CTL responses were seen in the group that underwent STI. These differences, although small, are statistically significant, but still do not demonstrate a clinical benefit of this strategy. In a field in which there has been little consensus, the consensus emerging from the meeting is that STI must remain in the research realm for the time being, and is not ready for clinical practice.

Other approaches to immune augmentation were also presented at the meeting. The use of IL-2 plus HAART clearly leads to greater increases in CD4+ cell count than HAART alone (Levy et al, Abstract 344), results in greater restoration of immune function to memory antigens (Durier et al, Abstract 345), and is associated with a greater increase in thymic production even in advanced patients (Saint-Mezard et al, Abstract 350). Long-term IL-2 therapy is able to maintain high CD4+ cell numbers, even when the frequency of administration is decreased (Chaitt et al, Abstract 347). However, clear demonstration of clinical benefit remains elusive. Coupling IL-2 therapy with treatment interruption may ultimately enhance the ability to see a beneficial effect, if one is induced (Smith et al, Abstract 360). IL-2 therapy along with HAART and HIV immunogen as therapeutic vaccine does induce T helper cell responses (Hardy et al, Abstract 349), but again clinical benefit of such strategies remains to be shown.

Conclusions

There seems to be little question now that the immune response plays a major role in containing HIV, even though it is ultimate-

Table **1.** Objectives of Supervised Treatment Interruption (STI)

Intended Objectives of STI	Clinical Setting
To enhance immune responses	Acute infection Chronic infection
To limit drug toxicities	Acute infection Chronic infection Treatment failure
To repopulate with wild-type virus	Chronic infection Treatment failure

ly unable in most cases to prevent disease progression in the absence of therapy. Encouraging results with early treatment of acute infection demonstrate that critical immune responses can be effectively boosted in infected persons and that the host-virus relationship can be manipulated. This finding should provide encouragement to continue to explore methods to obtain meaningful and durable immune enhancement as an adjunct to HAART in HIV infection. Moreover, the demonstration that control of viremia can be achieved following immunization offers further evidence that AIDS viruses can be contained by the immune system. Although a vaccine that prevents infection seems to remain an elusive goal, there appears to be a realistic hope that a vaccine to prevent or delay disease may become a reality.

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From Talk to Action in Fighting AIDS in Developing Countries

At the opening session of the 8th Conference on Retroviruses and Opportunistic Infections, Jeffrey D. Sachs, PhD, discussed the politics and global economics of HIV/AIDS. Addressing the audience of HIV researchers and clinicians, Dr Sachs offered specific policy recommendations for fighting the pandemic. An edited transcript of his lecture is included here. Please see page 14 for a subsequent consensus statement prepared by Dr Sachs and colleagues at Harvard University following the Retrovirus Conference.

We are at a pivotal time in the AIDS pandemic in terms of the role of science and the role of the United States. It is absolutely stunning for me as an economist to listen to and observe the stupendous progress of science in this area, including the basic science of the immunology and pathogenesis of the disease and the applied sciences that have brought us remarkable new pharmaceutical products and at least potential vaccines down the road. At the same time, I compare this with what I would regard as the utter failure of international policy to address this crisis in the poor countries of the world.

The essence of Africa's HIV/AIDS crisis begins with its extreme poverty and therefore its inability to mobilize even the barest of resources to address any of the public health crises the continent faces. The AIDS pandemic comes on top of the millions and millions of lives that are needlessly lost to malaria, tuberculosis, respiratory disease, diarrheal disease, and micronutrient deficiencies, deaths that would be readily preventable with even the smallest amounts of money. But the world has turned its back on this reality for the last 20 years. The core of Africa's crisis in public health is that, at least since 1980, because of the nature of the global economy and nature of the developing country debt crisis that engulfed the continent and many other parts of the poor world, almost all of Africa has experienced a virtually total collapse of its public health systems.

We ask why Africa does not do more in this crisis, but it is important to remember that outside of South Africa the average per capita income in African countries is around $300 per person per year. Even if these countries, with heavy international debts that have not been forgiven during the past 20 years, had been able to mobilize 4% or 5% of their gross national product for public health, we would be talking about sums of $12 to $15 per person per year to address a disease ecology that is probably the most difficult in the world and was such even before the AIDS pandemic arose in the early 1980s. In sub-Saharan Africa, 600 million people have been living without effective public health systems for a generation or more. The international response on AIDS could not have been less—a few tens of millions of dollars and a lot of hand-ringing, but no real assistance.

In an analysis I published with my colleague Amir Attaran in *The Lancet* in January of this year, we reviewed the donor assistance data for HIV/AIDS during the last 15 years. If you take all of the rich countries together—the United States, Europe, Japan, and the other rich countries—they currently have a combined population of about 1 billion people and a combined annual income of about $25 trillion per year. And yet all of the rich world mustered only $70 million per year for HIV/AIDS in Africa between 1996 and 1998, the most recent data that are available. That translates to $3 per year per HIV-seropositive individual in sub-Saharan Africa. We have essentially done nothing. Last summer former President Bill Clinton went to Nigeria. In 4 different stops he announced the same $10 million US aid program for AIDS in Nigeria, a country of 120 million people. That $10 million was about 40% of the estimated $25 million cost of his trip. I had recommended as a matter of public policy that he just stay home and send $35 million instead.

No major donor agency, not the World Bank nor any of the international aid agencies, has yet acknowledged that there may be a case for the rich countries to help make available the basic treatments, and especially the antiretroviral therapies, that could save millions of lives. The World Bank, in publication after publication in the second half of the 1990s, talked about massive programs for AIDS without mentioning treatment. Prevention and community support—even financial support to help grieving households and to help enterprises understand how to replace dying workers—those were mentioned as part of the World Bank's agenda. But the notion that people might be treated to be kept alive was not even mentioned as an option in World Bank studies, reports, and recommendations up until several months ago. And even in the last couple of months, it is still not the case that that institution, which has launched a multicountry AIDS program for Africa (their MAP program) with $500 million as a first set of loans, envisages that that money should be used for antiretroviral treatment.

See page 14 for a Consensus Statement on Antiretroviral Treatment for AIDS in Poor Countries, prepared by Harvard University faculty.

So we somehow went through the past 20 years with an utter failure of the rich countries to understand that Africa's most basic developmental challenge was the millions of people dying needlessly each year of preventable or treatable diseases. We went through the last 15 years of the greatest pandemic in modern history without doing anything meaningful for the poorest countries. The World Bank made it through an entire decade making just 3 AIDS-related loans in Africa, one to Kenya, one to Burkina Faso, and one to Uganda. The other 46 countries in sub-Saharan Africa did not receive a single focused loan to fight this pandemic, whether for treatment or prevention or anything else. And of course it has not gone unnoticed in Africa or in other parts of the world that

Dr Sachs is Director of the Center for International Development and Galen L. Stone Professor of International Trade at Harvard University in Boston. He is also Chairman of the Commission on Macroeconomics and Health established by the World Health Organization.

the technological advances in antiretroviral therapy and treatment of opportunistic infections and the like have substantially improved the health of the rich country populations while they have been almost unavailable to the poorest countries. As a result, we are creating a world of even starker and more shocking divides than the world of just a few years ago. It is one thing to have a world in which people of the rich countries are earning $25,000 per year and the 600 million in the poorest of the poor countries are earning around $350 per year and many are at $200 per year, but it is quite another to have a circumstance where millions of people are dying before our eyes from diseases that could be treated with new products and drugs that could save their lives, and we know it. It is a very dangerous situation from all perspectives—ethical, public health, economic, and political. The pharmaceutical companies are beginning to understand the risk. They stand the chance of becoming public enemy number one in all corners of the world. They are not very popular in the United States and when one adds the massive international campaign against these companies now happening in many parts of the developing world, where the unhappiness and adverse publicity filters back to the US market as well, I think they have a great deal of cause for worry.

The fact that we have done so little and that we are so rich, the fact that African governments all over the continent, not to mention governments in other parts of the world, are seeing the cusp of this pandemic in their countries and are understanding the dangers vividly, make it conceivable that we could actually change the way we have approached the pandemic during the past 15 years. I want to suggest a strategy that could, for the first time since this pandemic began, face up to the realities in the poorest countries. And I do so appealing to you at this Conference, who know about this disease, have more expertise, could contribute more, and could create more credibility for a new approach than any other group in the world. We have a chance to reach the basic idea that the AIDS pandemic should be addressed with real resources and that it should be addressed comprehensively, with prevention tied to treatment and supported by long-term basic science research, applied research for new pharmaceutical products and vaccines, and urgently needed operational research to understand the dynamics of the pandemic in the places that are being crushed by AIDS, particularly in Africa.

We now have, among the National Intelligence Council, Central Intelligence Agency, the United Nations Security Council, and other fora, a recognition that this pandemic fundamentally threatens US interests, not to mention the vital interests of millions of people who are dying from disease abroad, as well as their dependents and their communities. It threatens our interests because Africa has no chance of development without a capacity to address the public health crises, including AIDS, tuberculosis, and malaria. This is finally being recognized and appreciated because of important activism around the world and because of the shocking spectacle of the United States having enjoyed $9 trillion of capital gains in the last decade (only $1 trillion of which has been lost in the last 9 months of stock market decline). We have gained a net of some $8 trillion yet our government was incapable of mobilizing more than pennies to address the pandemic. We are also arriving at a moment where we might do something because the pharmaceutical companies are unhappy about the current situation, as well they should be. They are, and I think wrongly, becoming public enemy number one. They are the target of a growing amount of activism, part of which they bring on themselves through misguided actions, such as taking South Africa to court.

> From 1996 to 1998, the combined annual income of rich countries was $25 trillion; to fight HIV and AIDS during that time, they gave sub-Saharan Africa $3 per HIV-infected person per year

I propose a modest set of steps that could make, for the first time since the pandemic began, a truly new course with the understanding that we are going to try to save the lives of people around the world. What has been missing so far is money, not the will of the pharmaceutical companies. Nine months ago, the leading 6 producers of antiretrovirals and UNAIDS agreed to a rough schema in which the pharmaceutical companies would substantially reduce the prices of these products from the $10,000 to $15,000 per year range in the rich country markets down to prices closer to production costs. Agreements with 2 countries, Senegal and Uganda, were reached in the following 8 months. A few others are in the works. We have learned what we all knew from the producers of generic drugs as a result of these negotiations: the production costs for a triple combination therapy that relies on nucleoside and nonnucleoside reverse transcriptase inhibitors is probably in the range of $500 per year, certainly well below $1000 per year. Whether it is 7% of the market prices in the rich countries or 5% or 3%, we cannot be sure, but it is a very, very small amount relative to the retail prices that were the reference point leading so many observers to think that it was impossible to treat Africans because there was no way of providing the interventions at reasonable cost. The generics producers have even offered prices that are below these, ranging from $1 per day to $500 or $600 per year, although these are claims that have not yet been proven by actual deliveries. But this process did not work from the point of view of the world community or the pharmaceutical companies because, although these deals have been made, no one is getting treated and the pharmaceutical companies find themselves in an even worse position now than 9 months ago.

The products are not moving for a very simple reason: Uganda cannot afford highly active antiretroviral therapy (HAART) even at $500 per year. Uganda and similarly placed poor countries could only afford treatment if the rich countries of the world helped pay for it—which has been the missing piece until now. And the pharmaceutical companies need to understand that this kind of negotiation has further undermined them because of the absence of the rich country governments participating in the deal. Now the companies have agreed to price discounts and explained how big their mark-ups are in the rich country markets, with patent protection giving the returns to allow for high rates of research and development in the future. But they have exposed this mark-up to political risk without solving the problem of actually getting people treated. This

leads me to believe that with one real but not insuperable step, we could quickly move to a new and quite fundamentally different situation. The rich countries, with a $70 trillion gross national product, have been putting about $75 million a year into Africa. With even tiny amounts relative to our national income, only a few billion dollars a year, we could introduce real preventive actions combined with the vital component of treatment.

Suppose that it is possible for pharmaceutical companies to provide these basic combinations at around $500 per year. Given the 2001 Department of Health and Human Services guidelines that treatment should be extended to symptomatic patients, we are talking about 3 or 5 million people in Africa at the outer limit right now, not the 24 million HIV-seropositive individuals. We know that if the drugs were available there would be a fundamental barrier in capacity to deliver. We do not have operational protocols, much of the continent lacks the most basically trained doctors, and most of the primary health sector of Africa has collapsed over the past 25 years, to the extent that it had existed even a quarter century ago. Realistically, therefore, if these protocols could be developed and adherence could be achieved—if operational research verifies the capacity to use HAART appropriately in the context of very low income populations and largely illiterate populations—antiretroviral drug resistance could be kept at a tolerably low level and it might be possible to scale up the reach of these interventions to 1 million AIDS sufferers in Africa within the next few years. If we did wonderfully with spectacular assistance from our schools of public health, our universities, our international agencies, maybe we could reach 3 to 5 million African AIDS sufferers in 5 years.

How much money would that cost? For the drugs themselves, money is hardly an obstacle. At $500 per year and perhaps falling, 2 million people can be treated for $1 billion per year. If that figure is doubled for the extension of capacity to reach those people, then $2 billion per year reaches 2 million AIDS sufferers within 3 or 4 years. What is $2 billion in the scheme of things? To a macroeconomist, it is a rounding error. We are currently debating whether our tax cuts should be $2 *trillion*. It took me years to get UNAIDS to use the "B" word (billions). When they finally started talking about billions, all of the rest of the world, the rich world, had started talking about the "T" word. We are talking about $2 trillion in tax cuts extended over the course of the decade in our $10 trillion economy. With 1 billion people in the rich world, $2 billion is a levy of $2 per person per year. For $25 trillion of annual income, it is one 100th of 1% of gross national product; 1 penny out of $100 is the cost of taking the steps to provide HAART to people who are dying by the millions right now.

Let me suggest therefore what I think could be done and what I hope such powerful voices as yours could convey should be done with the power and backing of your scientific genius and your institutions. Any realistic program for this pandemic must combine prevention, treatment, and research as a starting point. There can be no effective prevention without treatment. When HIV-seropositive status is a death sentence, a sentence of utter exclusion from society because there is no treatment, there is also no effective prevention. So prevention and treatment are complementary forces. UNAIDS estimates that effective prevention interventions in Africa, including those for mother-to-child transmission and condom use for commercial sex workers and other core groups in the transmission of the disease, might cost around $2 or $3 billion per year to scale up for the 49 countries of sub-Saharan Africa. HAART could probably be brought to 1 or 2 million people within 3 years, with an annual cost of $1 or $2 billion per year.

> A levy of $2 per person per year in the rich world would provide antiretroviral therapy to approximately 2 million Africans with AIDS

How do we therefore make the breakthrough to the $5 billion that would amount to $5 per person per year in the rich countries? I suggest the following steps, which are feasible but still lacking the necessary US leadership. Without question, for African countries with an average income of $300 per year in Africa, there is no way to contemplate the use of these drugs or any effective treatments and prevention without ample support from the rich countries.

The first step therefore is for the United States to acknowledge that if HAART and related interventions were demonstrated to be medically effective, the United States and the other rich country partners would provide funding to the poorest countries in the world.

Step number two would be for the pharmaceutical companies to acknowledge the point that they have actually already acknowledged: that they would be prepared to supply these drugs at cost for such an international program. Pharmaceutical companies are not the obstacle right now. But what the pharmaceutical industry is realizing is that, without US government leadership, they cannot act effectively and they will continue to be in the line of fire.

The hard part is not getting the pharmaceutical industry to agree to supply a $500-per-year 3-drug regimen. The hard part is to get the underlying financing available to make that possible. What would the pharmaceutical industry like in return? They would like to preserve their rich-country markets, and we should be strong supporters of that. This is a remarkable and dynamic industry. It has the country's highest productivity in research and development, and therefore bashing of the industry is doubly unfortunate as we ride the cusp of our current scientific revolution in biotechnology and genomics. The idea that the pharmaceutical industry should be the villain rather than the hero of the story makes no sense. I am sure they are thinking the same thing, so we are not far from getting the buy-in of the pharmaceutical industry.

The third step is where you, as clinicians and researchers, come in, and that is to test the proposition that HAART could be applied and could be feasibly extended with medical and public health efficacy in the poorest countries of the world. For example, Paul Farmer at Harvard University has dedicated much of his life to treating some of the poorest people in the world in the central plateau of Haiti over the last 18 years. For the first 15 of those years he was treating mainly tuberculosis and other public health crises. In the last 3 years his practice in the central plateau has increasingly expanded to the introduction of HAART into one of the world's poorest and most difficult places. He is saving lives in this region and demonstrating, at least on a small scale, a remarkable efficacy of the treatment.

He has developed what I call DOT HAART, a system in which the poor indi-

viduals who are illiterate and living in villages without electricity, communications, or even roads have their therapy directly observed by local community health workers whom Farmer has trained. So Paul Farmer is taking DOTS, directly observational therapy shortcourse, from tuberculosis care and applying it as DOT, directly observed therapy, for HAART interventions, and what he has demonstrated is the capacity on a scale of dozens of patients to achieve extremely high adherence and extremely high efficacy in the intervention. What we need to know is what kind of protocols can work in these extraordinarily difficult settings. Do we need viral load monitoring? Do we need CD4+ cell counts? Is a non-protease inhibitor regimen feasible and for how long? What will be the dynamics of drug resistance? What kind of adherence can be achieved? What kind of DOT program or alternative program could be implemented? How fast could we train doctors? Suppose that we encourage Bill and Melinda Gates to put in internet connections in primary health centers all through Africa. Will you be at the other end of the e-mails helping to train the doctors that are doing the HAART interventions?

There are many, many practical questions for which we do not know the answers. Therefore not only do we need to start with a general concept that the rich countries are prepared to go forward and that the pharmaceutical companies are prepared to provide the drugs at cost, but also that we need to embark on this in a deeply and fundamentally scientific manner, viewing the next steps as operational research at the largest scale.

What I would like to see happen in the most concrete sense is for the World Bank to use its new multi-country AIDS program to put aside $50 or $100 or $200 million, as grants rather than loans, for HAART scale-up trials and for the National Institutes of Health, the Centers for Disease Control and Prevention, our medical schools, our schools of public heath, and other related institutions to be deeply involved with those projects so that we get a proper epidemiological analysis. We need to view this as a scientific intervention to examine feasibility. We can only approach the feasibility of large-scale use of HAART in Africa as a hypothesis—not as a proven conclusion but as a hypothesis—that needs to be tested urgently.

I would also recommend, just as a small footnote, that the World Bank set aside perhaps $50 million or $100 million to allow nongovernmental organizations, such as Medécins Sans Frontières or Farmer's Partners in Health, to apply for these drugs for use in small-scale trials in local units where these organizations are working. The funding should be based on scientific submissions so that the requests are not simply to "give us drugs" but are part of large-scale field trials that are extended to many parts of the African continent and perhaps to many other poor countries as well.

All of this could be done very quickly. We have talked for 15 years, and at least since the advent of HAART, we have talked for 5 years of pure hand-ringing about doing something. We now know that at least we can try to do something. We now know that at modest cost, if we are lucky enough that this works out, we could even bear the load of a dramatically expanded treatment intervention system for the world's poorest countries. What we need to do urgently is finally to move, to get started on some large-scale trials, to get the principals set out, to get the donor agencies to shed their economically illiterate and morally untenable position not to discuss treatment, and to get the process moving.

We need to embark on the provision of antiretroviral therapy in Africa in a deeply scientific manner, viewing the next steps as operational research at the largest scale

This is a good time to do it. The perhaps ironic feature of our new Presidency is that the new President will talk less than the old one but the old one actually accomplished nothing in regard to antiretroviral treatment. The new one will give confidence to the pharmaceutical industry to play a much more ambitious role. This government is a friend of the pharmaceutical industry and the industry knows that this government is not going after their markets, is not going for price controls, is not going to undermine their intellectual property rights. It is therefore possible for major pharmaceutical firms in the HIV field to come forward to help lead a new process so that they stop being the villains and start being the heroes, so that they make their drugs available, so that the drugs will not be the limiting factor, and so that the operational capacity and the research knowledge should properly be the limiting factor, because that is the one part of the process that is the hardest and that is the one we most urgently need to learn about.

AIDS is not the only crisis that the poorest countries are facing. Malaria continues to take at least more than 1 million and, by my estimates, more than 2 million lives per year. It is resurging, perhaps on the back of the AIDS pandemic. Tuberculosis and the other major killer diseases are equally under-addressed in Africa right now. They are much cheaper than AIDS to address and we understand much better what to do about them, but the fight against these diseases is also starved for cash. This country needs therefore not only to spearhead an HIV/AIDS program for the world, but also programs to help save millions of lives from the ravages of tuberculosis, malaria, and other killers, and thereby establish a humane base for the poorest countries of the world to begin once again their process of economic development, a process that has been completely and utterly derailed by the disastrous 20 years of public health failure. This will cost the rich countries perhaps $10 to $20 billion per year, of which the $5 billion per year for AIDS is just 1 part. But even as much as $20 billion would be less than one tenth of 1% of the gross national product of the rich countries. Given that we have stopped most foreign aid in our country, aside from the money that goes to the Middle East, one tenth of 1% of the gross national product is probably the very least that we should be doing to fight the great disease pandemics in Africa.

Thank you again for all of the wonderful science and medical knowledge that you are bringing forward. I hope you can use your positions, your expertise and your good offices to push forward a campaign for global justice.

Special Contribution

Consensus Statement on Antiretroviral Treatment for AIDS in Poor Countries

***By Individual Members of the Faculty of Harvard University*[1]**
(Signatories at end)

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.

The signers of this Consensus Statement 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.[2] Falling prices of antiretroviral 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.

The signers 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.[3]

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.[4,5] 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 antiretroviral 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% 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.[4] 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.[6]

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 2 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 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.[4]

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.[7-9] 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).[4,10] Without family support, these children often cannot 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.[4] 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 5 in 2020.[11] This demographic shift may contribute directly to increased 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 2 or 3 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.[16-18] New classes of drugs, the protease inhibitors and nonnucleoside reverse transcriptase inhibitors, allowed for more potent 3-drug antiretroviral regimens. These regimens, known as 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%) mother-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 6 years have plummeted in the United States and other wealthy countries (Figure 1).

Current US government recommendations suggest treatment of all individuals with moderately advanced to advanced HIV infection using HAART regimens of 3 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 combina-

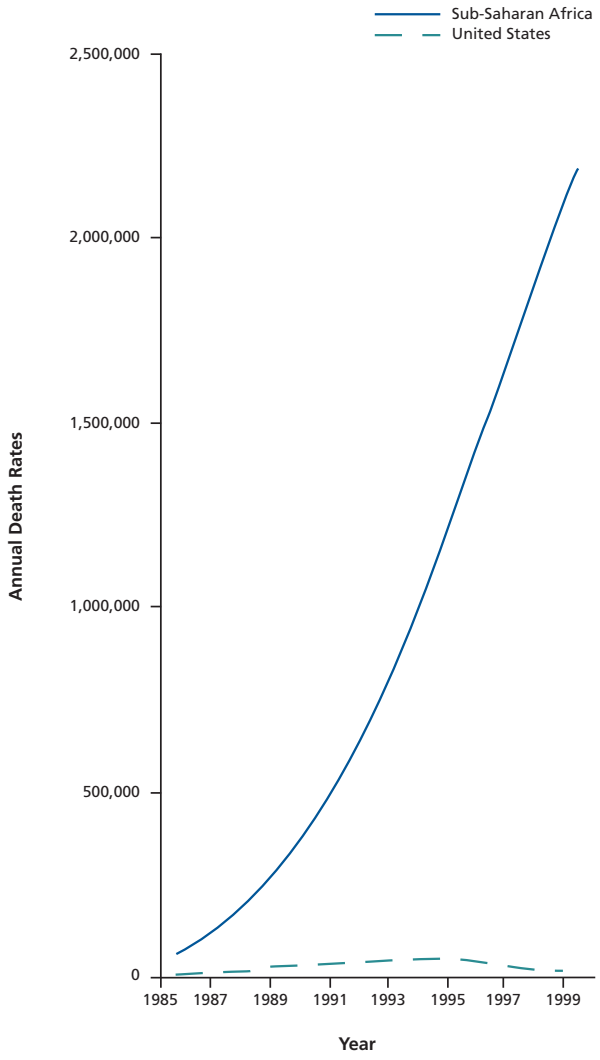

Figure **1.** Trends in age-adjusted AIDS death rates, 1985 to 1999. Shown are annual AIDS deaths for sub-Saharan Africa (solid line) and the United States (dashed line). In the United States, highly active antiretroviral therapy (HAART) was introduced in 1995, accounting for the visible decline in deaths. 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. Adapted from UNAIDS.

tion 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. A few middle-income developing countries, notably 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 1 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]

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 (ie, 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, which 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.[29-31] In Senegal, 86 patients have been treated in a pilot program for over 2 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 to 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 virologic, immunologic, 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 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 US guidelines, for example, recommend initiating HAART at CD4+ counts less than 350 cells/μL 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+ count 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 (eg, 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 several large-scale countrywide trials, to be conducted initially over a period of about 3 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 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+ count 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 is 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 United States 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 3 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 (eg, didanosine, efavirenz) and others in development (eg, 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 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 suboptimal in wealthy nations, such as the use of only 1 or 2 nucleoside reverse transcriptase 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 tuberculosis.

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: eg, 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.

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 (eg,

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 (ie, 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 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 3 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 4 countries—Côte d'Ivoire, Rwanda, Senegal, and Uganda—with nearly 20 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-$1850 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, 2 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 announced its decision to offer 2 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 all of these companies to assist in this effort. Based on these and other recent price quotations, and evidence on production costs, we estimate that a typical HAART regimen may cost as little as $500 a year, in large volumes.[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, 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 $1123/patient-year in sub-Saharan Africa. Assuming that 1 million patients in sub-Saharan Africa will receive treatment within 3 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 3 million people in sub-Saharan African countries could become HAART recipients within a 5-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 Africa 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% 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% higher than the African costs. Thus, in 3 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 accompanied by scaling up tuberculosis treatment as well, especially since tuberculosis is the leading opportunistic infection related to AIDS in Africa.

Beyond the 5-year horizon, the cost to the donor community will be subject to 3 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 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 5-year horizon. We do believe, though, that the first 2 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 US 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 2 principles:

i. All project proposals should originate in the recipient country by the government or a nongovernmental 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 Web site 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 mother-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 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 $1100 per patient per year, the total cost of treatment for 1 to 3 million HIV-infected individuals in Africa within 3 to 5 years would be easily managed by the world's wealthiest countries. Even at the 5-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 1¢ of each $100 of income in these economies. Extending this program worldwide would add around 25%, 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.

ANNEX A
Estimating the Cost of Expanded AIDS Treatment in Africa

As the main text of the Consensus Statement makes clear, low-income countries (ie, 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 (eg, 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 $4400 (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 is 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 (eg, medications, including antiretroviral drugs and drugs for opportunistic infections) and operational requirements (eg, research and clinical operations) for AIDS treatment. We estimate that as of today, Africa would represent approximately 80% of the global needs for donor support and that remaining donor support would assist countries in South and Southeast Asia (eg, India, where nearly 5 million people are infected with HIV) and in the Americas (eg, 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% 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 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 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, 3 million will test positive for HIV, with 1 million candidates for treatment. The breakdown is as follows:

Initial screening tests
(10 million people) × ($10/person) = $100 million (1-time cost)

Confirmation of HIV-positive status
(3 million people) × ($10/person) = $30 million (1-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 3 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]

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 $1000 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 1 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:

DRUG: (1 million people) × ($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 1 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, 3 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 nongovernmental health systems, either as they exist now or as they might exist in the next 3 to 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 100-fold increase in the number of such patients receiving HAART today.

3. Directly Observed Therapy (DOT) Costs

If the drugs are administered through directly observed therapy, additional costs will accrue. For DOT in Haiti, an *accompagnateur* (ie, 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: (1 million people) × ($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+ cell counts 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: (1 million people) × ($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 Community Programs for Clinical Research on AIDS (CPCRA), HIVNET, the Veterans Affairs 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:

RESEARCH: (50,000 people) × ($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: (1 million people) × ($650/patient-year) = $650 million/year

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

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

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

TOTAL = $1.123 billion/year

We conclude that the total cost of treatment, comprising the above expenditures, would be approximately $1123/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 $1123 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+ count 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 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 2 outcomes are compared as a ratio, or cost per unit of life expectancy. More advanced cost-effectiveness analyses compare 2 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 countries, compared not only to other HIV interventions but also to interventions for a variety of diseases and conditions.[24] 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 $1123/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.[64,65] 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.

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 US income, and sometimes higher.[66] On this basis, medical interventions that save a life-year at a cost of 2 to 3 times the average income (ie, an intervention cost of $70,000 to $105,000, given the average US 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.[24] Given the lower treatment costs in Africa, HAART in Africa is likely to be about 15 times more cost-effective than HAART in the United States, and 50 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 $1100 per life-year saved would also fall within the conventional bounds of 2 to 3 times the 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 5 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% to this cost, bringing the total donor needs to around $1.4 billion annually during the first 3 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 investment in the economic, social, and political well-being of the world's resource-poor countries, those that have been hardest hit by the scourge of AIDS.

Signed by Individual Faculty of Harvard University, below, in March 2001. (Alphabetical Order)

Gregor Adams, Marylyn Addo, Anna Aldovini, Marcus Altfeld, Deborah Anderson, Kwame Anthony Appiah, Amir Attaran, Dennis Ausiello, Daniel Barouch, Nesli Basgoz, B. J. Beck, Barry R. Bloom, David Bloom, Steven Boswell, Diana Brainard, Christian Brander, Hermann Bussmann, Steven B. Calderwood, Arese Carrington, Arachu Castro, Bruce Chabner, Tao Cheng, Hsiu-Ching Chang, Pride Chigwedere, Raymond Chung, Kenneth S. Cohen, Lisa Cosimi, Clyde Crumpacker, Richard D'Aquila, Ronald Desrosiers, Raphael Dolin, John P. Doweiko, Max Essex, Paul Farmer, Wafaie Fawzi, Harvey V. Fineberg, Jay A. Fishman, Kenneth A. Freedberg, Dana Gabuzda, Rajesh Gandhi, Henry Louis Gates, Jr., Ralf Geiben-Lynn, Peter Gilbert, Anne E. Goldfeld, Sue J. Goldie, Gilberto Gonzales, Philip J. R. Goulder, Steven Grinspoon, Jerome E. Groopman, Sofia Gruskin, George Hanna, Stephen C. Harrison, Jody Heymann, Howard Hiatt, Martin S. Hirsch, Lisa Hirschhorn, Wenzheng Huang, Michael D. Hughes, David Hunter, Elizabeth L. Hohmann, David Ives, R. Paul Johnson, Spyros A. Kalams, Phyllis Kanki, Kenneth Kaye, Elliot Kieff, Jim Yong Kim, Robyn Klein, Anne Klibanski, Irene Koulinska, Stephen W. Lagakos, Mark Lallemant, Georg Lauer, Sophie Le Coeur, Tun-Hou Lee, Eric Leire, Howard Libman, Judy Lieberman, Norman Letvin, Andrew H. Lichtman, Shahin Lockman, Yi Chen Lu, Andrew D. Luster, Harvey J. Makadon, MD, Richard Marlink, Stephen Marks, Joseph Martin, James J. Mongan, Monty Montano, Joia Mukherjee, Marian Nuetra, Philip Norris, Vladimir Novitsky, Victor Pena-Cruz, Trevor Peter, Richard Platt, Alvin F. Poussaint, Mark Poznansky, Allison Quayle, Kirthana Ramanathan, Michael R. Reich, Boris Renjifo, Gregory Robbins, William Rodriguez, Eric S. Rosenberg, Robert I. Rotberg, Jeffrey D. Sachs, Paul E. Sax, David T. Scadden, George Seage, Roger Shapiro, Henry J. Steiner, Megan Sykes, Deborah Prothrow-Stith, Ibou Thior, Cecile Tremblay, Ruth Tuomala, Peggy Ueda, Tonya L. Villafana, Rochelle Walensky, Frederick Wang, Zhengyu Wang, Bruce D. Walker, William Wester, Don C. Wiley, Preston N. Williams, Mary E. Wilson, Michael T. Wong, Jonathan Worth, Sigal Yawetz, Kimon Zachary, George Zeidenstein, and Edwin Zishiri.

Correspondence may be addressed to:
Amir Attaran, DPhil, LLB, email: amir_attaran@harvard.edu; or Martin S. Hirsch, MD, email: hirsch.martin@mgh.harvard.edu.

Footnotes and References

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; or of *Topics in* HIV *Medicine* or the International AIDS Society–USA.
2. This document should be construed with the understanding that its focus is AIDS treatment, and not AIDS prevention, which is a separate topic in its own right. The authors intend no negative comment on the value of prevention by this editorial choice. As the document makes clear, it is the authors' belief that treatment must go hand in hand with scaled-up prevention efforts, and that in so doing, treatment can help to augment the efficacy of concurrent prevention efforts.
3. Africa accounts for around 80% of all HIV infections in low-income or high-prevalence countries. As of end-1999, UNAIDS estimates that 24.5 million 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).
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66. 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 2 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 2 times annual income.

Pathogenesis and Treatment of HIV-Associated Nephropathy

At the International AIDS Society–USA course in Atlanta in February, Paul E. Klotman, MD, summarized the characteristics of HIV-associated nephropathy and discussed recent findings that indicate a direct role of HIV in causing renal disease and that suggest that the kidney may be a viral reservoir.

HIV-associated nephropathy (HIVAN) has become the most common single diagnosis in HIV-infected patients with renal insufficiency. More than 90% of patients with HIVAN are black, with 50% having a history of injection drug use. Data from 1999 indicated that AIDS-associated end-stage renal disease (ESRD) was the third most common form of ESRD in blacks aged 20 to 64 years (after diabetes and hypertension), accounting for 8% of cases.

As a clinical syndrome, HIVAN is characterized by significant proteinuria and a rapid progression to ESRD; there is evidence, however, that potent antiretroviral therapy may slow the progression of the disease, and a greater number of patients with HIVAN are living longer following therapy. The disease has tended to occur in later-stage HIV infection, but cases of early onset have been seen and there is considerable interest in identifying renal changes that are associated with HIVAN early in the course of HIV infection. The disease is characterized by normal to enlarged kidneys on gross appearance and histopathologically by microcystic tubular disease with focal segmental glomerulosclerosis, frequently with glomerular collapse, and swelling of visceral epithelial cells on light microscopy.

No evidence of immune complexes is seen in the vast majority of cases. Biopsy in HIV-infected patients with proteinuria finds the typical features of HIVAN in about 60% of cases, and a variety of other disease entities are also found in association with factors such as hepatitis and drug use (Table 1).

Dr Klotman is Professor of Medicine and Chief of Nephrology at Mount Sinai Medical Center in New York City.

Pathogenesis

A central question in the pathogenesis of HIVAN is whether the disease can be attributed to direct viral effects or to HIV-related changes in the cytokine milieu. Increasing evidence supports a direct role of HIV. Studies in a transgenic mouse model (Tg26), in which HIV-1 envelope and regulatory genes are expressed but *gag* and *pol* genes are deleted to render the virus noninfectious, have shown that renal disease in these animals closely resembles HIVAN; the resulting disease includes rapid progressive renal failure with the HIVAN features of microcystic changes and segmental sclerosis, including the collapsing variant. These findings that viral expression in the kidney is sufficient for the development of the disease suggest a direct role of HIV in its pathogenesis. Such findings, however, do not explain the strong predilection for disease in blacks.

To determine whether HIV is indeed present in the human kidney, Dr Klotman and colleagues have studied biopsy specimens from patients with HIVAN. Their research has involved using polymerase chain reaction (PCR) for long terminal repeat (LTR) circular forms of HIV (nonintegrated species that are thought to be degraded), which indicate recent nuclear import of the virus; in situ hybridization for messenger RNA (mRNA), which indicates ongoing viral transcription; and in situ DNA PCR to detect integrated proviral DNA.

> More than 90% of patients with HIVAN are black, with 50% having a history of injection drug use

Studies with PCR for LTR circular DNA showed the presence of this marker for recent cellular infection in approximately half of samples tested, including samples from patients with no detectable HIV in the peripheral blood (Figure 1A). Use of HIV-1 *gag* mRNA probes to determine whether such infection was occurring in renal cells (ie, rather than in T cells or macrophages within the samples) found HIV-1 mRNA in the perinuclear region of renal tubular epithelial cells and glomerular cells, with clustering of positive cells apparently indicating efficient cell-to-cell transmission of the virus (Figure 1B). In situ PCR for HIV-1 DNA in these samples showed proviral infection of the nuclei of both tubular epithelial cells and podocytes in the glomerulus (Figure 1C).

Table **1.** Diagnoses in HIV-Infected Patients with Proteinuria

- 60% have typical features of HIV-associated nephropathy on biopsy
  - Focal segmental glomerulosclerosis and microcystic tubulointerstitial disease
- Other common diagnoses
  - Focal segmental glomerulosclerosis alone (additional 10%-15%)
  - Membranoproliferative glomerulonephritis (10%)
  - Tubulointerstitial diseases (7%)
  - Minimal change disease (5%)
  - Membranous glomerulopathy (4%)
  - Lupus-like nephritis (3%)
  - Amyloidosis (3%)

Adapted from D'Agati and Appel, *Semin Nephrol,* 1998.

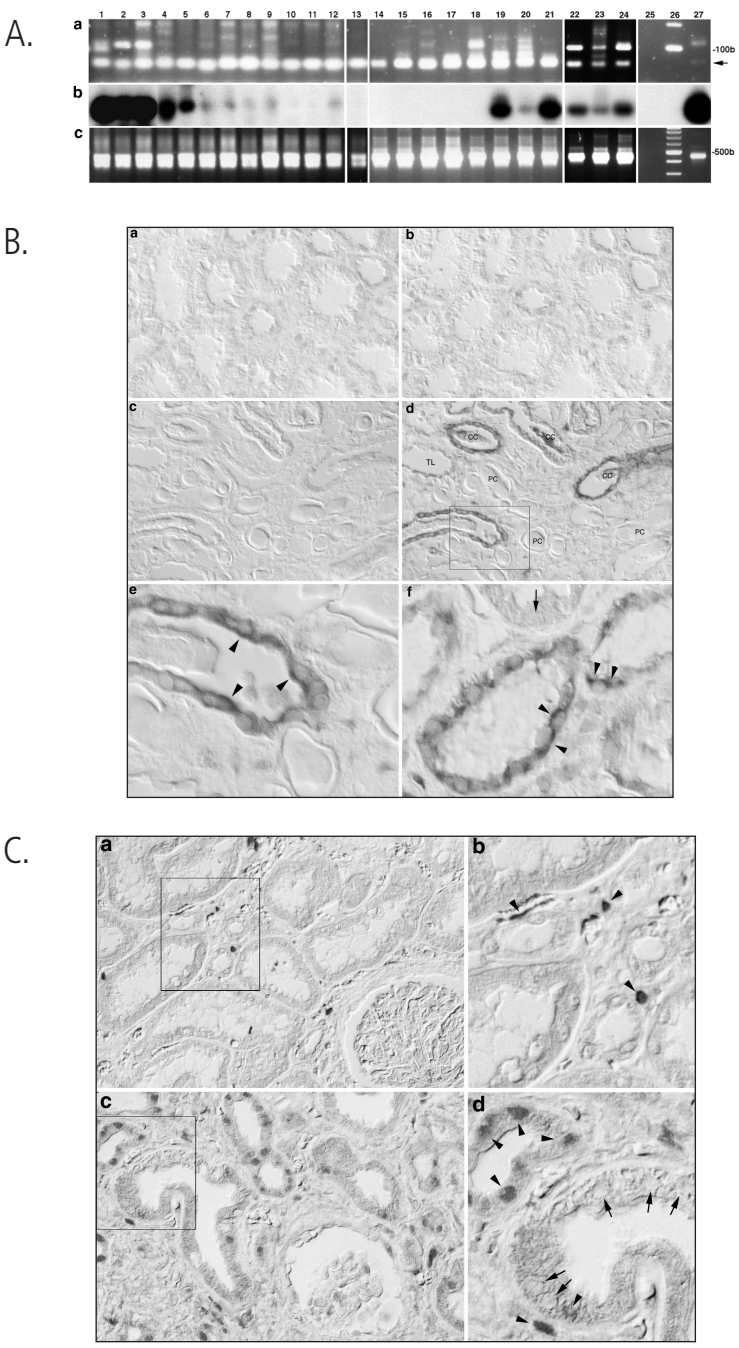

Figure **1.** Findings in renal biopsies in patients with HIV-associated nephropathy: (A) long terminal repeat circular DNA; (B) HIV messenger RNA; and (C) in situ polymerase chain reaction for HIV DNA. Adapted from Bruggeman et al, *J Am Soc Nephrol,* 2000.

In subsequent studies, laser capture microscopy has been used to isolate renal epithelial cells shown to have integrated virus by in situ PCR to permit amplification of viral envelope V3 loop genetic sequences. These studies have found that the genetic variants of the virus in the kidney are distinct from the genetic variants in the peripheral blood of the same patient. This evolutionary divergence within patients suggests the presence of different selective pressures within the kidney.

The results of studies that have used markers for cell differentiation and proliferation suggest that viral infection in renal cells is associated with a loss of differentiation and an increased proliferation of podocytes and tubular epithelial cells. In summary, these studies have shown the presence of active viral replication in the renal cells of patients with HIVAN, and the finding of viral genetic material in samples from patients with no detectable HIV RNA in the peripheral blood at least suggests that the kidney could be a reservoir for HIV.

Treatment

No standard therapy for HIVAN has been developed, but there is evidence that potent antiretroviral therapy has a beneficial effect on disease progression. Angiotensin-converting enzyme inhibitors are sometimes used in patients with HIVAN, but their effects have not been evaluated in controlled studies. Steroids have also been reported to be of benefit in some cases, but the rationale for using them in a disease that is not immune complex-mediated is not clear.

The effects of potent antiretroviral therapy on HIVAN have yet to be examined in a controlled study; protocols for investigating this are currently being reviewed by the AIDS Clinical Trials Group. In the absence of data from controlled trials, Dr Klotman's group has generated a mathematical model for assessing the impact that potent therapy may have had on the increase in prevalence of ESRD in HIV-infected black patients. In brief, this model shows that the decrease in the prevalence of ESRD that can be attributed to HIVAN since 1995 can be explained by the introduction of potent antiretroviral therapy. The best fit of the existing data demonstrates that potent therapy has had an estimated 28% efficacy in reducing the increases in the number of HIV-infected black patients with ESRD. This model also predicts that, in the absence of drug treatment with 100% efficacy and with increases expected in the pool of patients at risk for developing HIVAN (ie, black patients who are HIV-seropositive or living with AIDS), the size of the population of HIV-infected patients with ESRD will continue to increase.

Anecdotal evidence of a beneficial effect of potent antiretroviral therapy on very early onset HIVAN comes from the recent experience of Dr Klotman and colleagues in a patient who presented with ESRD during acute HIV seroconversion. Biopsy performed when the patient was about to undergo dialysis showed classic features of HIVAN, consisting of microcystic disease and focal segmental glomerulosclerosis. The patient was given aggres-

sive antiretroviral therapy, and plasma HIV RNA level was suppressed to levels below detection limits. After 3 months the patient's renal failure had completely resolved. Repeated biopsy showed reversal of the microcystic changes that were present before potent antiretroviral therapy was initiated and resolution of collapsing glomerular disease with residual scarring. Collagen staining showed residual interstitial fibrosis, but it was markedly improved from the pretreatment condition. Assessing LTR circular viral DNA in biopsy samples found marked positivity before potent antiretroviral therapy, but not after. In addition, the resolution of renal failure after potent therapy was accompanied by a restoration of podocyte differentiation (as indicated by increased synaptopodin staining) and normalized cell proliferation (as indicated by normalized Ki67 marker positivity). In situ hybridization for viral mRNA, however, showed that some (low) level of viral transcription was ongoing.

Observations in this patient suggest both that renal damage due to active infection may be seen early in the course of HIV infection and that potent antiretroviral therapy may have a beneficial effect on the course of HIVAN by stopping such damage, thus making structural and functional reconstitution possible. In addition, the finding of ongoing viral transcription in the absence of active cellular infection during potent antiretroviral therapy supports the hypothesis that the kidney may be a viral reservoir; it remains unclear, however, whether the kidney might be a source of viral repopulation when the efficacy of potent antiretroviral therapy in suppressing viral replication is reduced or when drug pressure is removed.

Suggested Reading

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Update on Drug Resistance Mutations in HIV-1

A subgroup of the International AIDS Society–USA Resistance Testing Guidelines Panel has been convened to maintain a current database of HIV drug resistance mutations. The most recent update is provided.

In May, 2000 the International AIDS Society–USA Resistance Testing Guidelines Panel revised its recommendations on resistance testing in HIV-1 infection (Hirsch et al, JAMA, 2000), first published in 1998. The Resistance Testing Guidelines Panel continues to monitor the field to assess when updates are merited. Data continue to accumulate about the role of resistance testing in clinical practice. These new data tend to further support the recommendations published in 2000 and do not yet appear to warrant revising the current guidelines.

The 2000 guidelines included a list of mutations commonly associated with antiretroviral drug resistance, which has become widely used by clinicians involved in HIV medicine. To maintain a current list of mutations that impact drug susceptibilities, a subgroup of the Resistance Testing Guidelines Panel has been convened. This subgroup, the Resistance Mutations Project Panel (see sidebar), under the leadership of Drs Richard T. D'Aquila and Jonathan M. Schapiro, met at the 2001 Conference on Retroviruses and Opportunistic Infections in Chicago, Illinois.

The mutations figures have been updated here. A major change since the 2000 publication is that the distinction between primary and secondary has been removed for mutations in reverse transcriptase. The clinical significance of the mutations that appear first (ie, primary) versus those that appear later (ie, secondary) remains debatable, particularly for nucleoside reverse transcriptase inhibitors (nRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). In general, the clinical effects of many of these mutations overlap. Therefore the panel has decided, at this point, to suspend the use of the concept "primary versus secondary" for the reverse transcriptase inhibitor group as a whole. As a general rule, the magnitude of resistance increases as the number of mutations increases.

The distinction between primary and secondary mutations was kept for the protease inhibitors, because in the protease gene, those mutations that are listed as primary do have greater effects on drug susceptibility (eg, increasing the median inhibitory concentration [IC_{50}]) than do those that are listed as secondary. Other major changes include:

- A new investigational class of drugs, the nucleotide reverse transcriptase inhibitors, has been added. Tenofovir is currently available through an expanded access program.
- Mutations that affect the efficacy of lopinavir/ritonavir, which was recently approved by the US Food and Drug Administration (FDA), have been added.
- Mutations that lead to cross-resistance within the reverse transcriptase inhibitor and protease inhibitor classes have been added.

These figures will be updated regularly and be available on the International AIDS Society–USA Web site, www.iasusa.org, and through HIV InSite, http://hivinsite.ucsf.edu.

The Resistance Mutations Project Panel has begun to build a database of references (peer-reviewed, published articles and conference abstracts) that address the effect of mutations on drug susceptibility. When completed, the interactive database will be available online and will provide, for each mutation or mutation pattern represented in the mutations figures, the citation that demonstrates its clinical impact. The site will allow users to search the scientific literature using several identifiers (eg, mutation, class of drug, study type, authors). Other important issues will also be addressed on the site in the future, such as the interactions between mutations and the impact of drug levels on the effects of specific mutations in clinical settings.

The launch of this Web site will be announced in *Topics in* HIV *Medicine* and at www.iasusa.org. Comments on the current mutations figures can be addressed via e-mail to "resistance@iasusa.org."

Resistance Mutations Project Panel

The current members of the Resistance Mutations Project Panel, a subgroup of the Resistance Testing Guidelines Panel, are:

Chair
Richard T. D'Aquila, MD
Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

Vice-Chair
Jonathan M. Schapiro, MD
National Hemophilia Center, Yair, Israel, and Stanford University School of Medicine, Stanford, California

Françoise Brun-Vézinet, MD, PhD
Hôpital Bichat-Claude Bernard, Paris, France

Bonaventura Clotet, MD, PhD
Hospital Universitari Germans Trias I Pujol, Barcelona, Spain

Brian Conway, MD
University of British Columbia, Vancouver, British Columbia, Canada

Lisa M. Demeter, MD
University of Rochester, Rochester, New York

Victoria A. Johnson, MD
The University of Alabama at Birmingham, Birmingham, Alabama

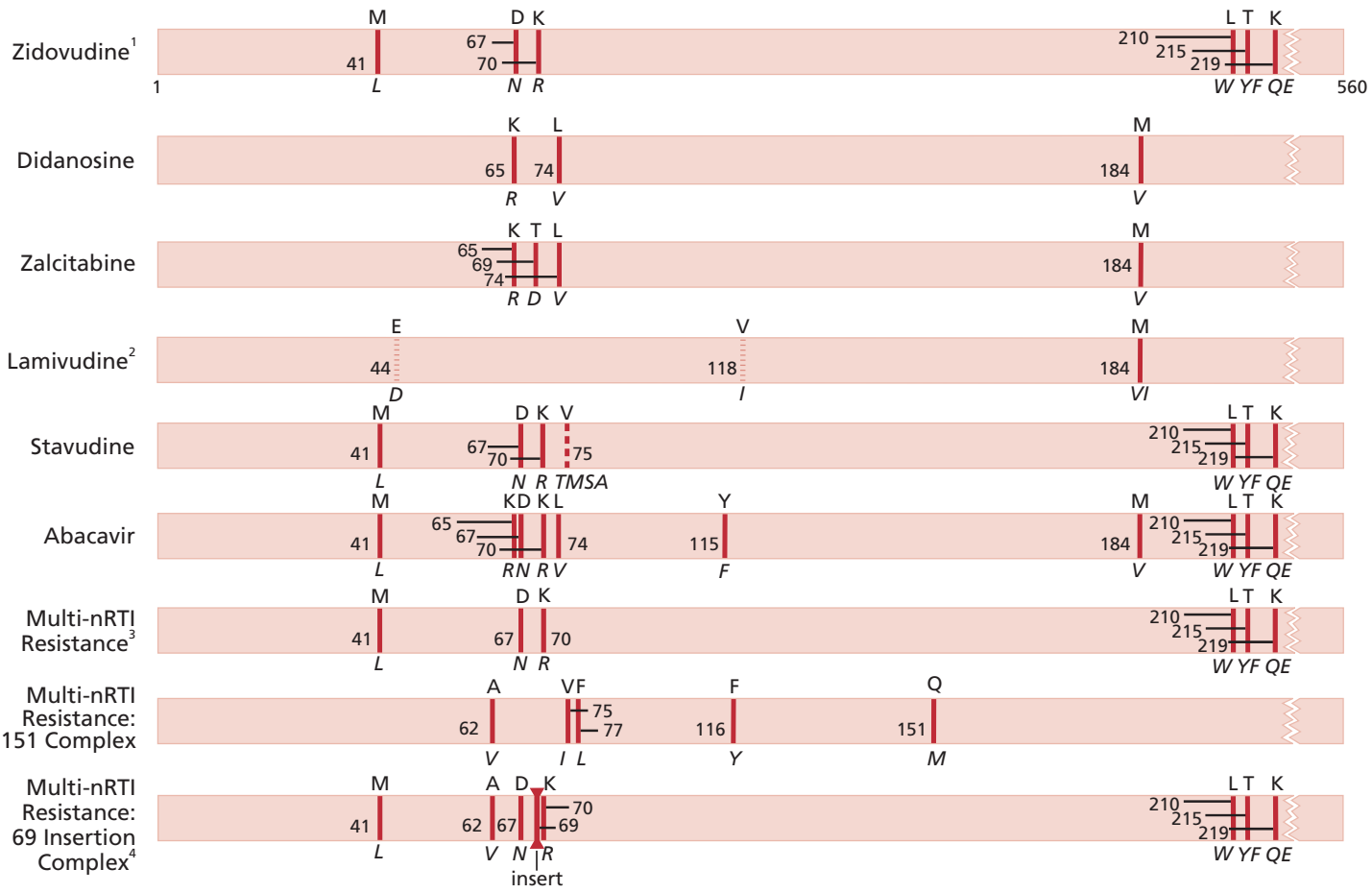
Daniel R. Kuritzkes, MD
University of Colorado Health Sciences Center, Denver, Colorado

Clive Loveday, MD, PhD
The Royal Free Hospital School of Medicine, London, England

Douglas D. Richman, MD
University of California San Diego and San Diego Veterans Affairs Medical Center, La Jolla, California

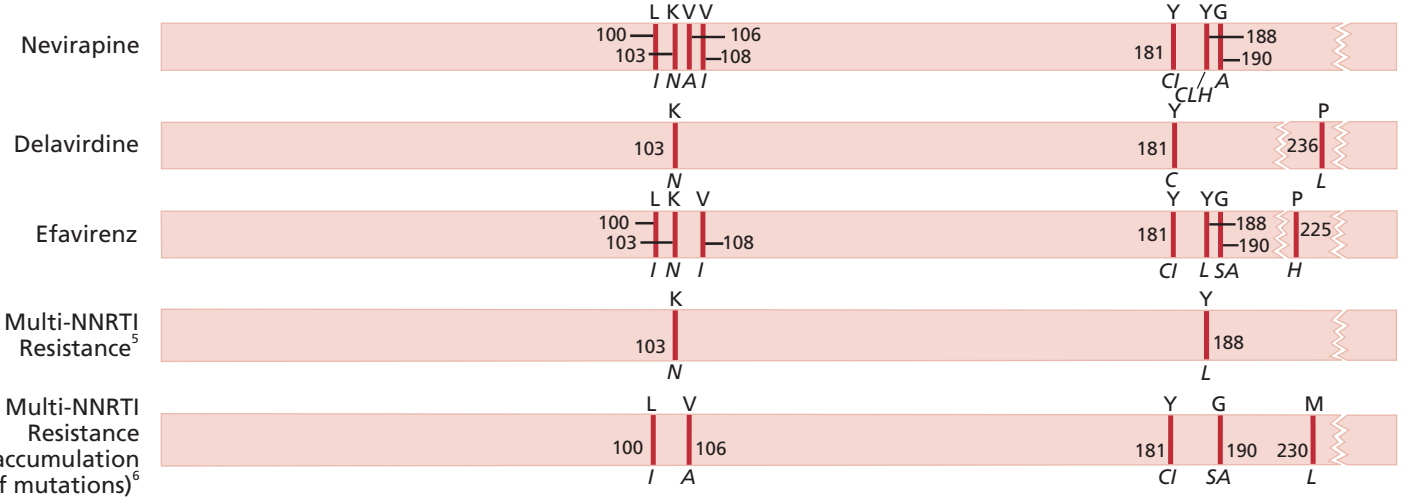
MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside Reverse Transcriptase Inhibitors



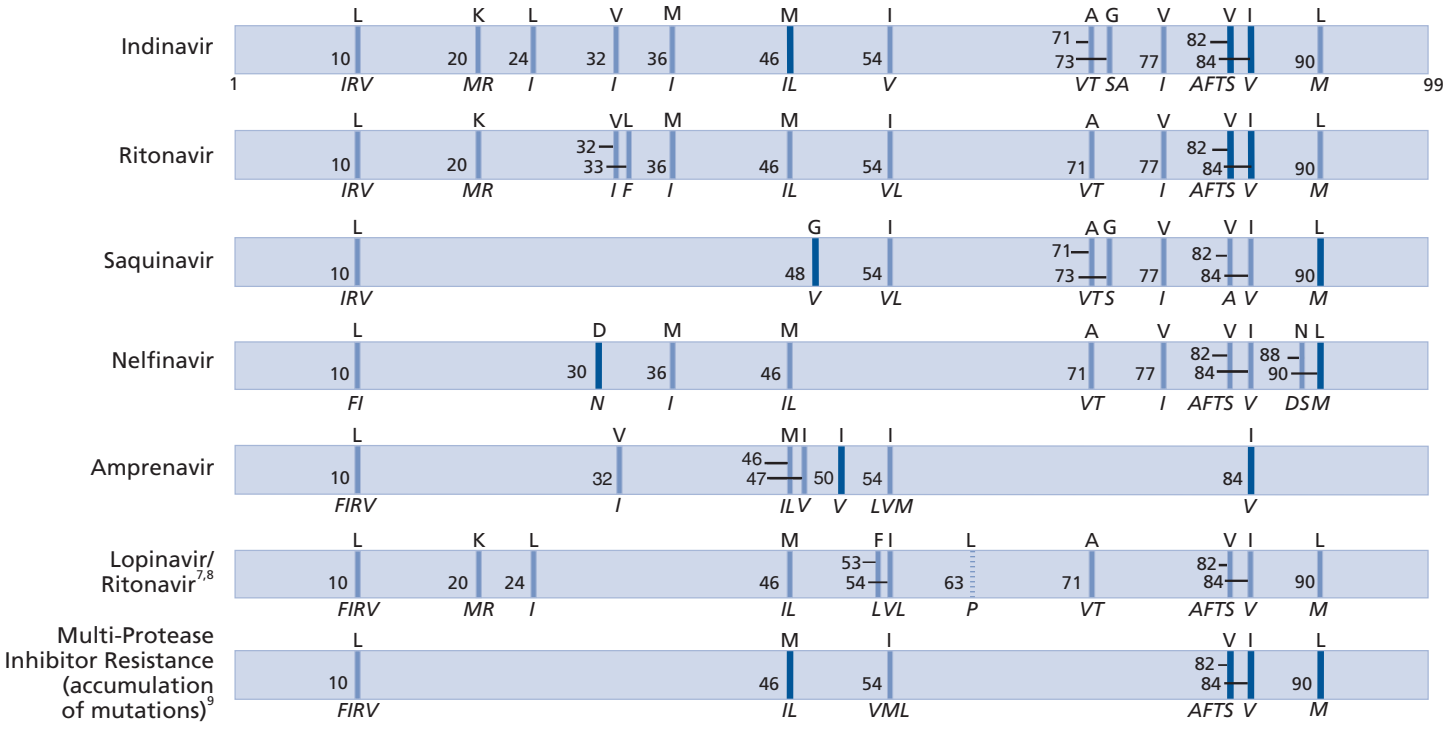
Nucleotide Reverse Transcriptase Inhibitor (currently available under expanded access program)

Nonnucleoside Reverse Transcriptase Inhibitors



MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO PROTEASE INHIBITORS

Protease Inhibitors



For each amino acid residue, the letter above the bar indicates the amino acid associated with wild-type virus and the italicized letter(s) below indicates the substitutions that confer viral resistance. The number shows the position of the mutation in the protein. The mutation selected in vitro with stavudine (red dotted bar) is rarely seen in patients having treatment failure. For indinavir, the mutations listed as primary may not be the first mutations selected, but they are present in most patient isolates in combination with other mutations. Mutations selected by protease inhibitors in Gag cleavage sites are not listed because their contribution to resistance is not yet fully defined. The figures are adapted from Hirsch et al, JAMA, 2000. Updated April 2001.

Amino acid abbreviations are: *A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.*

Footnotes

[1] Reverse transcriptase mutation M184V may temporarily partially reverse the effects of the mutations shown here on zidovudine susceptibility. However, if more than 3 of the listed mutations are present, the additional presence of M184V is not likely to reverse phenotypic zidovudine resistance.

[2] One article reports increased low-level phenotypic resistance to lamivudine with E44D and/or V118I mutations, in the absence of a concurrent M184V mutation (Hertogs et al, *Antimicrob Agents Chemother*, 2000). One abstract (D'Arminio-Monforte et al, 8th Conference on Retroviruses and Opportunistic Infections, 2001, Chicago, Abstract 447) reported no association over the short term between E44D or V118I and viral load responses to a lamivudine-containing combination regimen.

[3] Mutations associated with cross-resistance to nRTIs (except lamivudine).

[4] The 69 insertion complex, consisting of a mutation at codon 69 (typically T69S) and followed by an insertion of 2 or more amino acids (S-S, S-A, S-G, or others), is associated with resistance to several nRTIs. The 69 insertion is often accompanied by mutations at other sites.

[5] K103N or Y188L by itself can substantially reduce the clinical utility of all currently approved NNRTIs.

[6] Accumulation of these mutations (2 or more) substantially reduces the clinical utility of all of the currently approved NNRTIs.

[7] The accumulation of 6 or more of these mutations is associated with a diminished response to lopinavir/ritonavir. The accumulation of 7 or 8 or more of these mutations makes a response to lopinavir/ritonavir unlikely. The mutations listed are based on one report (Kempf et al, 4th International Workshop on HIV Drug Resistance and Treatment Strategies, 2000, Sitges, Spain, Abstract 89) and no primary mutations have yet been identified. Further clinical experience and research are needed to better define the mutations that affect the effectiveness of lopinavir/ritonavir.

[8] Protease mutation L63P is common in viruses that have never been exposed to protease inhibitors (Kozal et al, *Nat Med*, 1996), and may be more prevalent in viruses from patients in whom a protease inhibitor-containing regimen has failed. However, by itself, protease mutation L63P does not cause any appreciable increase in the IC_{50} for any protease inhibitor. L63P is listed for lopinavir/ritonavir (and not any other protease inhibitor) because the prescribing information approved by the FDA lists it as one of the multiple mutations that together predict a lack of viral load response to lopinavir/ritonavir-containing regimens.

[9] Accumulation of these mutations (4 or 5 or more) will likely cause multi-protease inhibitor resistance.

Social, Cultural, and Epidemiologic Considerations in HIV Disease Management in US Latino Populations

The increasing burden of HIV disease among Hispanic populations in the United States and measures for improving HIV-related health services to Latinos were discussed by Felix F. Carpio, MD, MPH, at the International AIDS Society–USA course in Los Angeles in February.

Of the total of more than 46,000 cases of AIDS in adolescents and adults reported in the United States in 1999, nearly 9000 were in Hispanics, more than 21,000 were in non-Hispanic blacks, and nearly 15,000 were in non-Hispanic whites. The disproportionate burden of AIDS cases among Latinos is shown by the fact that Latinos accounted for 19% of AIDS cases and 13% of the US population on 1999 estimates. The disproportionate effect is even greater among blacks, who accounted for 47% of AIDS cases while constituting 12% of the US population in 1999; whites accounted for 32% of AIDS cases and 71% of the population. Overall, the AIDS case rate among Latino men is 58.2 per 100,000 population, 3.27 times that in white men, and that in Latino women is 16.6 per 100,000, 6.9 times that in white women. In some locales, AIDS rates in Hispanics are 10 or more times higher than in whites. It is currently estimated that 110,000 to 170,000 Latinos in the United States have HIV infection.

Transmission of HIV in Latinos

That Latino populations are generally clustered in certain geographic areas and that the infection rates in some of those areas are high mean that HIV infection is likely to continue to increase in Latinos. As shown in Figure 1, the mode of exposure in Hispanics with AIDS in 1998 was predominantly injection drug use in those who were born in Puerto Rico and predominantly through men having sex with men in those who were born in other areas of Latin America or in the United States.

According to a study by Marín and colleagues (*Fam Plann Perspec*, 1993), it appears that having several sexual partners is less common in Latino women than in white women, but more common in Latino men than in white men. Latinos generally reported low use of condoms with their primary sexual partners and higher use with their secondary sexual partners (partners outside of marriage or casual partners). The prevalence of homosexual or bisexual activity in Latino men in the United States has been reported to be 3% or less, but this is likely a gross underestimate.

Latinos account for 24% of the cases of AIDS in the United States that are related to injection drug use. The prevalence of injection drug use in Latinos is high, particularly in New York, New Jersey, and other East Coast states; it appears to be lower in California, where injection drug use accounts for less than 10% of the cases of HIV infection. The rate of infection with HIV also appears to be higher in Latino injection drug users than in their white counterparts, possibly because of the greater use of shooting galleries and needle sharing by Latinos, particularly in East Coast areas. Greater access to and use of injection drugs in association with greater poverty also contributes to the higher transmission rates.

Another factor in transmission in Latinos is needle sharing in the use of injectable medications and vitamins in the home. Many drugs that are available only by prescription in the United States are available over the counter in Latin American countries, and Latinos in the United States, particularly California, Florida, and New York, frequently obtain and use these medications. Increased suspicion for transfusion-related infection is also warranted, since appropriate screening of blood products has been implemented slowly in Latin American countries.

Social and Cultural Elements in Infection Risk and Treatment

Poverty is a strong factor in the epidemiology of HIV infection in Latinos, in whom the rates of poverty and unemployment are increasing. The poverty rates are higher in Latino families than in black or white families, and even many intact Latino families in which both adults work face economic hardship. The poverty rate in Hispanics in the United States is highest in Puerto Rican families, at 37.5%, followed by Mexican American families (25%), Central and South American families (22.2%), and Cuban families (13.8%); for comparison, the poverty rate in non-Hispanic families is 9.5%. With poverty come conditions that also confound pre-

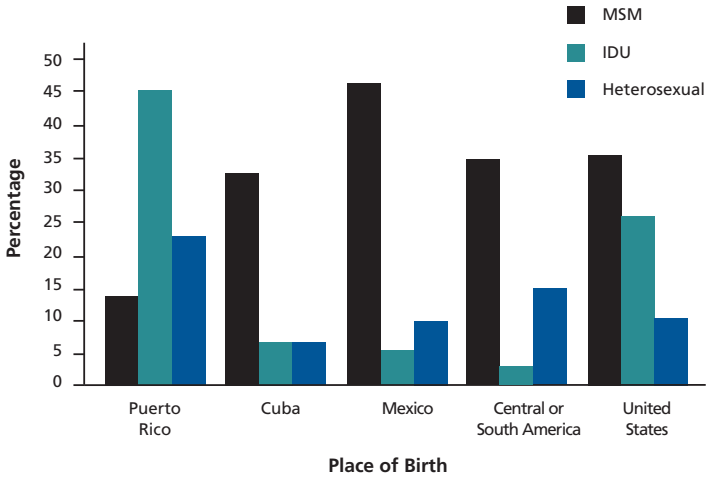


Figure **1.** Mode of exposure to HIV in US adult Hispanics with AIDS, 1998, by place of birth. Most heterosexual cases are in women who have sex with injection drug users (IDUs), HIV-seropositive men, and bisexual men. MSM indicates men who have sex with men. Adapted from the Centers for Disease Control and Prevention, available at: http://www.cdc.gov/hiv/pubs/brochure/latino-report.pdf.

Dr Carpio is Associate Medical Director of HIV Services at AltaMed Health Services, in Los Angeles.

vention and obtaining adequate health care, such as the use of illicit drugs, violence, economic dependence, lack of adequate housing and nutrition, and lack of health services and insurance and drug-treatment and prevention programs.

Development of effective programs for managing HIV disease in Latinos requires the consideration of the above factors and of a number of cultural values, lack of recognition of which can impede or undermine treatment efforts. Ideally, health care services in this setting should be designed

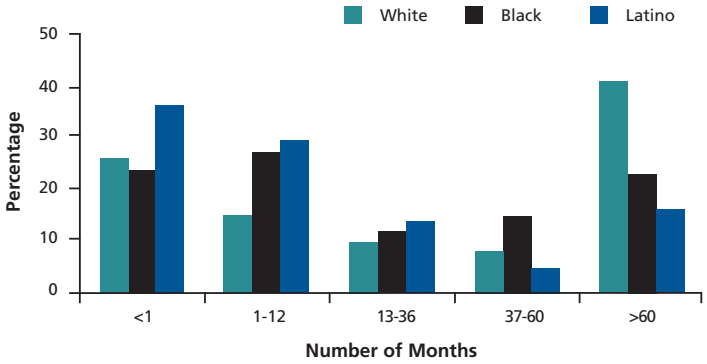


Figure **2.** Time between patients' learning of HIV-seropositive status and diagnosis of AIDS, Los Angeles County, 1997-1999, by ethnicity (Supplemental HIV Surveillance Study Project). Adapted from HIV Epidemiology Program, Los Angeles County, Department of Human Services, January 2000.

Thirty-six percent of the Latinos with AIDS in Los Angeles County received the diagnosis within a month of learning that they were HIV-seropositive

and delivered by Latinos who speak both Spanish and English and who are more likely to understand the cultural issues involved in relating to Latino patients. Many of the cultural values that must be taken into account in health care have been identified through research in prevention programs in Latino communities in California. They can be summarized as *familismo*—emphasis on the family as the primary social unit and source of support; *simpatía*—the importance of smooth social relations, emphasis on politeness and respect, and rejection of assertiveness, negative behaviors, and criticism; *personalismo*—the preference for relationships that provide familiarity and warmth; and *respeto*—the need to feel respected and valued in interactions with health care providers. In addition, many Latinos may not have a linear view of time: rigid timing or scheduling is not as important as attending to personal relationships, and the hurried pace in the health care setting may be perceived as rudeness. In addition, Latinos are often uncomfortable in discussing sexual matters; sex is considered private and personal, and it is often not even discussed by sex partners. The beliefs of Latinos about gender roles include the expectation that men should be "sexual beings" and should pressure their partners for sex. There is also a considerable degree of 'homophobia' among Latino men, with sex between men being viewed as unacceptable, and fewer Latino men consider themselves homosexual or bisexual than do men of other racial and ethnic groups.

HIV Health Care

Access to health care is an important issue in Latino communities. In Los Angeles County, for example, Latinos with HIV disease enter the health care system at later stages of the disease than do patients of other racial and ethnic groups. The times between a diagnosis of HIV-seropositivity and a diagnosis of AIDS in Latino, black, and white patients in Los Angeles County in 1997 through 1999 are shown in Figure 2. The proportion of patients in whom AIDS was diagnosed within 1 month after they had learned that they were HIV-seropositive is higher in Latinos than in blacks and whites. AIDS was diagnosed within 12 months after they had learned that they were HIV-seropositive in 65% of Latino patients and after more than 60 months in only 16%.

Reducing the Burden of Disease

A number of measures for reducing the burden of HIV disease in Latinos can be recommended. Educational programs in HIV disease specifically for Latino care providers and other providers who work with Latino patients should be developed and implemented. Peer-led Latino-focused programs for treatment education and adherence support should also be developed, expanded, and improved. In addition, the pool of bilingual and bicultural HIV-related health, mental health, and social service providers in Latino communities should be expanded through educational programs and incentives. Culturally competent and language-appropriate intensive interventions in prevention for diverse Latino populations also should be funded and expanded. In addition, migrant populations should be targeted through outreach programs.

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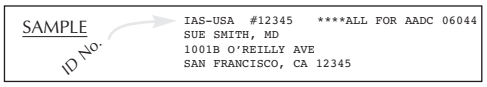

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