

Antiretroviral Therapy Where Resources Are Limited

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In the State of the Union address of January 2003, President George W. Bush announced an unprecedented five-year, \$15 billion Emergency Plan for AIDS Relief¹ to provide highly active antiretroviral therapy (HAART) to up to 2 million patients infected with the human immunodeficiency virus (HIV) in Africa and the Caribbean. Such efforts are urgently needed to offer hope to the more than 24 million HIV-infected persons living in settings where medical and economic resources are limited. The availability of generic HAART formulations has facilitated efforts mediated by the Joint United Nations Programme on HIV/AIDS (UNAIDS) to encourage multinational pharmaceutical manufacturers to provide HAART at discounted prices.² Some have argued that access to effective therapies for HIV-infected persons should be one of the highest global public health priorities.^{3,4} However, it is important to recognize that simply providing affordable access to these drugs is insufficient. The global objective should be to combine prevention with access to clinical care that clearly helps patients to live longer, healthier lives.

The Global Fund to Fight AIDS, Tuberculosis, and Malaria was created to increase the global resources available to combat these three infectious diseases, which continue to kill millions of people in developing countries. The initial round of funding was announced in April 2002, with a total of \$378 million allocated over a period of two years to support 40 programs in 31 countries.⁵ The fund provides an opportunity to address a number of challenges to ensure that when antiretroviral drugs are more accessible, they will be used in a rational and beneficial way for patients. In addition to affordable drugs, health care providers will be needed who know how to incorporate antiretroviral therapies into comprehensive clinical care plans. Affordable access to laboratory assays necessary for the safe and effective use of antiretroviral therapies is also required. In addition, guidelines must be developed for the use of antiretroviral therapies that have clearly been shown to benefit patients with HIV in developing countries. Finally, efforts to provide HAART should be incorporated into primary care programs, as part of HIV-prevention, education, and counseling activities.

THE NEED FOR TRAINED HIV CARE PROVIDERS

There are now 19 antiretroviral drugs approved by the Food and Drug Administration for the treatment of HIV infection that can have potentially serious side effects and interactions with other drugs.^{6,7} Decisions about when to start HAART, when to change therapy, and which drugs to prescribe have become increasingly complicated. Safe and effective use of HAART in North America requires measurements of plasma viral load and CD4+ T lymphocytes, as well as monitoring for viral resistance and adverse drug reactions. The increasing complexity of the care of HIV-infected persons is reflected in the frequent updating of clinical care guidelines.^{6,7} In the United States, it has been shown that the survival of patients is dependent upon the experience of their physicians in treating HIV-infected persons,⁸ and that experience should inform the current discussions about providing access to antiretroviral drugs to developing countries. The introduction of HIV-treatment programs in those countries offers the opportunity to increase the number of providers with access to the training and information required for the safe and effective use of HAART.

INFRASTRUCTURE REQUIREMENTS FOR THE USE OF HAART

As noted above, current North American and European clinical care guidelines incorporate measurements of plasma HIV load and CD4+ T lymphocytes and testing for viral resistance as essential tools for the rational, effective use of HAART.^{6,7} Countries with limited resources lack the laboratory infrastructure and trained technicians to perform these assays. Complete blood counts, liver-function tests, and serum creatinine and lipid levels are routinely used in assessing patients for adverse drug reactions. Efforts to expand access to HAART should be accompanied by a more evidence-based approach to optimize HIV care guidelines for local settings. This approach will require adequate laboratory and clinical infrastructure to collect the evidence. Alternative, low-cost methods for moni-

toring patients receiving HAART are a public health priority. In addition, the predictive value of lower-cost clinical end points, such as those recently used in Haiti, needs to be evaluated.⁹

ANTIRETROVIRAL RESISTANCE

There is increasing evidence that resistant strains of HIV are being transmitted in North America and Europe as a result of the difficulty of completely suppressing viral replication.¹⁰⁻¹² The World Health Organization (WHO) has responded to this concern by establishing the Global HIV Drug Resistance Surveillance Network to assist countries in monitoring for the emergence of HIV drug resistance.¹³ Antiretroviral agents must be introduced in a way that ensures a sustainable drug supply in order to avoid the early pitfalls seen in the Ivory Coast and Gabon, where erratic therapy resulted in high levels of drug resistance.^{14,15} Apart from early treatment failure, resistant strains of HIV may rapidly abrogate the effectiveness of zidovudine, lamivudine, and nevirapine for the prevention of vertical transmission of HIV; this is currently among the most important global HIV interventions.

IMPROVING TREATMENT GUIDELINES

Current guidelines from the Department of Health and Human Services, the British HIV Association, and the International AIDS Society recommend the initiation of HAART in asymptomatic HIV-infected patients with CD4+ T-lymphocyte counts of less than 200 cells per cubic millimeter (with treatment considered in patients whose counts are between 200 and 350 cells per cubic millimeter).^{6,7,16} Recent WHO guidelines have also adopted this CD4+ T-lymphocyte level for the initiation of HAART in asymptomatic patients in developing countries.¹³ The HAART guidelines were based on data from clinical trials in North America, Europe, and Australia and may not take into account genetic and geographic differences in the normal range of CD4+ T-lymphocyte levels in other countries.^{17,18} A potential limitation of the HAART guidelines for use in developing countries is that the clinical trials cited to support their recommendations show that HAART specifically affects mortality and clinical end points (e.g., *Pneumocystis carinii* infection and cytomegalovirus infection) in HIV-infected patients with CD4+ T-lymphocyte counts of less than 200 cells per cubic millimeter. It is unclear

whether these guidelines will be equally useful in settings where most of the morbidity and mortality associated with HIV is due to infections, such as tuberculosis and other endemic bacterial infections, that occur in patients with CD4+ T-lymphocyte counts that are greater than 200 cells per cubic millimeter.

In the light of the clear benefit of HAART in reducing HIV-associated mortality in developed countries, providing access to HAART for patients in developing countries is a humanitarian and ethical imperative. However, although current HAART guidelines are important and will assist initial efforts to provide access to HAART for those who need it most, these guidelines may not be optimal for HIV-infected patients in settings where medical and economic resources are limited. There may also be an ethical imperative to ensure that clinical care guidelines for the use of HAART in such settings are supported by the same evidence-based criteria required for U.S. guidelines. Efforts to provide access to drugs should be coordinated with other support to developing countries, in order to help them generate their own data to validate and modify guidelines for the use of HAART.^{19,20}

PROVIDING HAART

Until recently, access to HAART in many countries was limited to a handful of patients who could afford it. A few countries, such as Brazil, have initiated programs to expand access, and preliminary data suggest that the provision of HAART following North American and European guidelines can substantially reduce HIV-associated morbidity and mortality.²¹ Encouraging observational data have emerged from pilot programs of HAART in Haiti and South Africa. The program in South Africa showed that HAART reduced the incidence of tuberculosis associated with HIV type 1 by more than 80 percent.^{9,22} Uganda and Senegal have also demonstrated preliminary success with expanded HAART-access programs.²³⁻²⁵ Experience with HAART in North America, Europe, and Australia has taught us a number of important lessons that appear to be supported by the preliminary data from developing countries. Specifically, adherence to therapy is difficult, and suboptimal antiretroviral regimens that are not as effective as HAART may result in the rapid development of drug resistance. As more programs are introduced to expand access

to antiretroviral drugs, it is imperative to provide developing countries with the resources to measure their clinical effect.

HIV THERAPY COMBINED WITH
PRIMARY CARE AND PREVENTION

UNAIDS recently issued recommendations for the use of trimethoprim-sulfamethoxazole prophylaxis in all symptomatic HIV-infected patients in sub-Saharan Africa, on the basis of a study conducted in the Ivory Coast that showed a substantial reduction in the morbidity associated with common bacterial infections.^{26,27} The use of isoniazid prophylaxis has also been shown to improve survival in HIV-infected patients.²⁸ It is unclear which of the available interventions — expanded access to affordable HAART, isoniazid prophylaxis, trimethoprim-sulfamethoxazole prophylaxis, fluconazole prophylaxis, measles vaccination, pneumococcal vaccination, or provision of clean water — will have the greatest impact on HIV-associated morbidity and mortality in developing countries. Efforts to provide access to HAART that do not incorporate other cost-effective interventions into a comprehensive primary care plan could have a limited effect on morbidity and mortality among HIV-infected patients in such settings. Increasing access to preventive care and treatment of opportunistic infections remains an additional challenge. A proportion of the current global budget for HIV prevention and for the care of HIV-infected patients should be directed toward support of clinical trials of interventions to reduce HIV-associated morbidity and mortality in developing countries.

THE PRIORITIES

The global objective should be to provide access to therapies and care that reduce the morbidity and mortality associated with HIV infection. The effort to provide access to affordable antiretroviral drugs is an important step toward this objective, but there are a number of additional steps that should be taken. Along with advocating global access to affordable HAART comes the obligation to ensure insofar as possible that these drugs will directly benefit patients. Programs to expand access to HAART will provide a unique opportunity to improve overall health care delivery systems. Entire communities will benefit from the improved delivery of primary care, the integration of care and prevention pro-

grams, and the availability of trained, experienced health care providers.

The international health community must support the establishment of the infrastructure necessary for monitoring the clinical and public health effect of HIV therapy, including assessments of the effect of HAART on HIV-associated morbidity and mortality, which might be quite different from what has been found in developed countries. Adherence to treatment regimens and the development of drug resistance will need to be monitored. The sustained availability of drugs and the avoidance of suboptimal antiretroviral regimens are essential. In many settings, factors such as nutritional deficiencies and coinfections with endemic pathogens could affect immunologic and virologic responses to HAART.

It will also be important to monitor the effect of access to HAART on high-risk behavior and the transmission of HIV. With increased access to HAART, the developing countries must undertake further clinical research designed to optimize guidelines for the clinical care of HIV-infected patients in local situations. Failure to provide the resources necessary to train health care providers, ensure reliable laboratory monitoring, and optimize treatment guidelines may limit the public health benefit of global efforts to expand access to HAART.

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