

EDITORIALS



Scaling Up Treatment — Why We Can't Wait

Jim Yong Kim, M.D., Ph.D., and Charlie Gilks, D.Phil., F.R.C.P.

Many arguments have been raised over the years to justify not moving rapidly forward with antiretroviral treatment programs for people living with the human immunodeficiency virus (HIV) and AIDS in settings with limited resources. The standard litany included the price of therapy as compared with the poverty of the patient, the complexity of the intervention, the lack of infrastructure for laboratory monitoring, and the staggering lack of trained health care providers. Narrow cost-effectiveness arguments have been commonplace. False dichotomies — prevention or treatment, rather than both — have too often gone unchallenged. Perhaps of greatest concern several years ago was the ambivalence — if not the silence — of political leaders and experts in public health. The cumulative effect was to allow the death of tens of millions of poor people in developing countries who are living with and becoming ill as a result of HIV infection. Meanwhile, in countries rich in resources, HIV infection has largely become a manageable, chronic condition because of the availability of combination-drug antiretroviral treatment.

The inequity between rich and poor countries in terms of access to HIV treatment has rightly given rise to widespread moral indignation, and a few outstanding leaders have been consistent and courageous in their personal and public stances. The national program in Brazil has long shown what can be achieved when there is unswerving political commitment and public health leadership.¹ Some innovative projects pioneered by international nongovernmental organizations in diverse settings have clearly established that a very simple approach to antiretroviral treatment with intensive community engagement and support can achieve remarkable results.^{2,3} In 2000, the United Nations Accelerating Access Initia-

tive finally brought the research-based pharmaceutical industry into play and, with the rise in generic competition, drug prices have since fallen substantially.⁴ At the same time, fixed-dose combinations have become more widely available.⁵

Building on these lessons, the World Health Organization (WHO) has advocated a public health approach for treating people with HIV and AIDS in resource-limited settings. This approach proposes the use of standard first-line treatment regimens based on a simple five-drug formulary, with a more complex — and so far, much more expensive — set of second-line options.⁶ The steps in decision making for patients (the mnemonic is “the four S’s”: when to start, substitute for toxicity, switch for failure, or stop and move to end-of-life care) have been standardized, and intensive-training packages for health and community workers have been developed and implemented in many countries.⁷

These rapid advances in public health have been matched by unprecedented opportunities and funding through the President’s Emergency Plan for AIDS Relief (PEPFAR) in the United States, The World Bank, and the Global Fund to Fight AIDS, Tuberculosis and Malaria. In 2003, the lack of access to treatment was declared a global public health emergency by the WHO and the Joint United Nations Programme on HIV and AIDS (UNAIDS), and the two agencies launched the “3 by 5” initiative, with the ambitious, aspirational target of having 3 million people receiving antiretroviral therapy in developing countries by the end of 2005.⁸ Many countries have since set corresponding national targets and worked gallantly to embed treatment within their own national AIDS programs and health systems and to harness the synergistic connections between treatment for HIV and AIDS and preventive inter-

ventions. The recent communiqué from the Group of Eight, more commonly known as G8, endorsing universal access to HIV treatment by 2010 is another major step forward.

These encouraging advances mean that there can be no more excuses for not expanding global access to antiretroviral treatment. Solid progress has been made — with approximately 1 million people estimated to have been in treatment by June 2005 — although not at the desired pace.⁹

Certainly, significant challenges remain. Some skeptics doubt that a high standard of care can be provided by nurses and community health workers (rather than scarce highly trained physicians¹⁰), although this approach is now being used successfully in many countries. But we who have worked in developing countries know that in many settings that are poor in resources, adoption of a decentralized model of care is essential if health systems are to overcome serious human-resource constraints and move toward the goal of monitoring and supporting patients for life. Innovative strategies to support adherence may be required, but so far, adherence rates in even the most impoverished settings compare favorably with those of patients in the United States.¹¹ Drug-supply links are fragile in many countries, but concerted efforts are now being made to strengthen them, with potentially great benefits for the provision of other essential medicines. It is now clear that responding aggressively to HIV and AIDS is critical to reinforcing health systems as a whole and to achieving broader development objectives in the coming decade.¹²

The article by Severe et al. from the Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) project in this issue of the *Journal*¹³ is particularly important for the contribution it makes to the still-limited published literature on the scale-up of access to antiretroviral therapy in settings with limited resources. Port-au-Prince, Haiti, is one of the most challenging urban centers in the world in which to implement a major public health intervention. The results, as compared with those from settings in the United States, are truly remarkable. In a setting with only limited infrastructure and few staff members, over 1000 patients are now being treated. After one year of therapy, 87 percent of adults and 98 percent of children were still alive. Dropout rates were less than 8 percent, an

outcome that vindicates the decision to link the treatment program with nutritional supplementation and existing social programs. Of particular note is the estimated cost per patient in treatment per year: about \$1,600 with (largely generic) antiretroviral medications accounting for 35 to 40 percent of the total.

What are the tasks ahead for those of us working in these programs? In most countries where there is a high prevalence of infection with HIV and AIDS, the number of people in need of treatment still exceeds the capacity to provide it. Enrollment must be accelerated in both urban and rural settings, and sufficient quantities of good-quality, affordable antiretroviral medicines must be guaranteed. In the years ahead, keeping patients on treatment will be by far the greatest challenge, and information about evidence-based approaches and best-practice protocols for the management of chronic diseases in settings with limited resources is sorely needed. Adherence support, rather than regimen potency, may be the single most critical determinant of long-term success. Our overall efforts to combat the epidemic of HIV and AIDS must build on the pace and rhythm that countries have achieved already in their responses to the concrete treatment goals set first by PEPFAR and then by the WHO with the 3 by 5 initiative. Most important, we must bring a rapidly accelerated pace to our prevention efforts. We must move beyond pilot projects, set clear prevention targets that are time-limited, and dramatically accelerate our efforts in testing and counseling. The recent commitment from the minister of health in Lesotho to offer an HIV test to every person in his country in short order could build much-needed momentum and provide an example that should be replicated in other high HIV-burden settings.

It has often been said that our generation will be judged by our response to the HIV and AIDS pandemic. Although there is much more to do, the GHESKIO project and the responses from many other developing countries give us hope that the final judgment may be less harsh than we had feared.

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Rejection — More Than the Eye Can See

Terry B. Strom, M.D.

In comparing current clinical outcomes in renal transplantation with those of 30 years ago,¹ graft failure from immunologic factors and death from opportunistic infection in the first year after transplantation are no longer common clinical outcomes. The therapeutic regimens used today to prevent and treat rejection or infection among renal-transplant recipients bear only a small resemblance to those used 30 years ago.

In contrast, the diagnostic strategies used to detect rejection and distinguish it from other causes of renal dysfunction have not budged during the past two decades. A rise in the level of serum creatinine suggests allograft dysfunction, but the reasons can be elusive. Nephrotoxicity from immunosuppressive agents may cause acute and chronic allograft dysfunction, and accordingly, clinicians attempt to maintain drug levels in the therapeutic range. To aid in the resolution of the difficult differential diagnosis of allograft dysfunction, ultrasonography and renal biopsy are often performed.

This reactive diagnostic approach is often too late, and there are limitations because, first, drug levels do not test how therapy is affecting the recipient's immune response, and second, biopsies lack sensitive histologic patterns for the diagnosis of drug-induced nephrotoxicity and early rejection. Furthermore, detecting adverse host anti-graft immunity before there is evidence of graft dysfunction has not been feasible. Since the diagnosis of rejection is made after the advent of renal damage, it is not surprising that the neces-

sarily late application of antirejection therapy often results in only partial restoration of renal-transplant function. Serial surveillance biopsies of the transplant, a maneuver that would undoubtedly detect some instances of subclinical rejection,² are precluded by cost and complication-related issues.

The advent of reverse transcriptase polymerase chain reaction and DNA-microarray technology has allowed for highly sensitive, accurate, and quantitative detection of the transcriptional profiles of tissue samples from recipients³⁻¹² and donors,¹³ thereby enabling the discovery of a molecular signature for acute cellular rejection.³⁻¹² Acute allograft rejection is characterized by infiltration of the allograft by activated T cells. Accordingly, expression of T-cell-activation genes is evident in renal-transplant biopsy specimens obtained from patients who are undergoing transplant rejection.^{2,4-12} Knowing that activated donor-specific cytotoxic T lymphocytes (CTLs) infiltrate rejecting allografts, the expression of T-cell-activation genes that control the cytolytic machinery of activated CTLs was first analyzed in renal-transplant biopsy specimens.⁴⁻⁶

Since the transplant is infiltrated by a T-cell-rich population of mononuclear leukocytes, robust intragraft expression of the T-cell-specific T-cell antigen receptor⁷ and T-cell-specific CD3⁸ genes are excellent markers for rejection. Nonetheless, infiltration with other mononuclear leukocytes is also noted during rejection. Particularly interesting is the observation that amplified expression