



Patents versus Patients? Antiretroviral Therapy in India

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Legislation passed by the government of India rarely draws international attention, let alone global outrage. But in December 2004, to comply with the requirement of the World Trade Organiza-

tion (which India had joined in 1995) that its member countries adhere to trade-related aspects of intellectual property rights (TRIPs), the president of India issued a patent-amendment ordinance requiring 20-year patents on all new medications. The ordinance went into effect January 1, 2005. Objections were voiced around the world by advocacy groups for patients with human immunodeficiency virus (HIV) infection, who characterized the proposed law as pitting patents against patients. As a result, in March 2005, the Indian Parliament passed a more lenient bill — but one that could still pose major ob-

stacles for access to, and the development of, new generic drugs and that could stimulate lengthy litigation and increase the costs of new drugs substantially, thus threatening recent progress.

Over the past three years, a revolution in commitment, new funding, and price reductions for antiretroviral therapy has permitted expanded HIV-treatment programs to take root in many countries. The U.S. President's Emergency Plan for AIDS Relief (PEPFAR); the Global Fund to Fight AIDS, Tuberculosis and Malaria; the World Health Organization's 3 by 5 Initiative; the Elizabeth Glaser Pediatric AIDS

Foundation; and Médecins sans Frontières, among others, have paved the way for large-scale access. The unmistakable benefits of the efforts of these groups have included a reduction in suffering and death, a substantial decrease in the transmission of HIV to infants, and improved medical care in resource-limited settings.

Sustaining access to effective HIV drugs — and ensuring their affordability — is a central challenge faced by those who strive to roll out antiretroviral therapy. Experience has taught us that a formulary of antiretroviral drugs is needed to transform HIV infection from an inevitably fatal disease to a chronic illness. Frontline antiretroviral regimens work quite well for many patients but can have short-term and long-term toxic effects and can lead



Patients Awaiting Services in the Adult HIV Clinic of the Infectious Diseases Institute at Makerere University, Kampala, Uganda.

Antiretroviral therapy is provided through PEPFAR and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

to drug resistance that necessitates the use of new medications if the benefits are to be sustained. Data from high-volume outpatient clinics in the United States document the need for frequent changes in therapy. Many HIV-infected persons in the United States are alive today as a result of an expanded formulary, and they are dependent on the active pipeline of drug development for continued health.

In resource-limited settings, the focus of HIV-treatment programs has been to provide access as quickly as possible, for as many people as possible, to a first-line regimen. Generic drugs are chosen because of their low cost. In the late 1990s, the Brazilian government launched an ambitious program to provide universal access to antiretroviral therapy. The local production of generic antiretroviral agents generated great controversy over intellectual-property rights, but it withstood a

challenge from the U.S. government, which argued that such production infringed patent-protection agreements. This successful program now delivers therapy to more than 150,000 patients through the public health system and has impressively reduced HIV-related morbidity, mortality, and hospital and medical costs.

Generic antiretroviral agents are now being used in Africa and Asia as well, and many of them have been manufactured in India, where, since 1970, the Indian Patents Act has permitted the production of generic versions of drugs. Because only slight modifications in manufacturing could qualify a product for a new patent, Indian companies were able to offer HIV drugs at prices as low as 4 percent of those of brand-name drugs. The practice by Indian manufacturers of co-formulating antiretroviral drugs could reduce patients' pill burdens, the likelihood of dosage er-

rors, and theoretically, the risks of treatment failure and drug resistance. The new Indian patent legislation may well slow, if not threaten very substantially, the development of new products with these benefits.

What does all this mean for the millions of HIV-infected persons in current or imminent need of lifesaving antiretroviral therapy? Will patent laws and their application block the pipeline of anti-HIV drugs for resource-limited countries? Fortunately, the Indian response to TRIPs does not pose a short-term danger for current efforts to expand access to antiretroviral therapy. Drugs that are already in production are immune from the new patent regulations in India and may continue to be exported. Right now, this means that the most commonly used coformulated preparations of antiretroviral agents should continue to be available at reduced prices. Indeed, it is the other challenges to treatment programs — limitations of workforce, diagnostic tests, clinic infrastructure, and patient-monitoring tools — that represent the greatest immediate obstacles to these efforts.

Although the simple first-line antiretroviral regimens in wide use today clearly save lives, they may already be failing to meet all the needs of today's HIV-infected patients, a proportion of whom may be intolerant of, or have contraindications to, the available therapies. For example, concerns are increasingly being voiced about the widespread use of stavudine, given its propensity to cause peripheral neuropathy, stigmatizing lipoatrophy, and lactic

Courtesy of the Infectious Diseases Institute

acidosis. Alternatives are needed now to avoid these complications and the consequent disillusionment with large-scale antiretroviral rollouts that might ensue. Efavirenz carries a risk of teratogenicity for women of childbearing potential, and nevirapine can cause severe rash and hepatotoxic effects. Finally, treatment failure is occurring in resource-limited settings, and there is a growing need for medications outside the scope of the currently produced generic formulations. Without robust second-line therapeutic regimens, patients lose the benefits of antiretroviral therapy and may transmit drug-resistant virus to others, jeopardizing the efficacy of front-line regimens. Persons with HIV infection require decades of treatment, and the downstream consequences of a limited formulary will take on increasing importance over the long haul. "Sustaining" will soon surpass "scaling up" of antiretroviral therapy as the major challenge in some countries. Brazil is already facing this challenge, and African and Asian countries with far fewer resources will probably encounter even greater hurdles in gaining access to second-line therapies.

The risks posed by the TRIPs legislation to HIV-infected persons in resource-limited countries cannot be ignored, but there are solutions to this apparent conundrum. The simple fact is that we need to have it both ways. We need to encourage quality-controlled manufacturing of generic versions of current and future an-

tiretroviral agents, since this has proved to be the most efficient way to provide large-scale treatment at hugely discounted prices.

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At the same time, we need to provide incentives for major pharmaceutical companies to continue to develop antiretroviral drugs for the long-term benefit of HIV-infected people globally. Protection of intellectual-property rights and tiered pricing arrangements are key elements in maintaining this commitment.

Although this paradox may seem insurmountable, there are already indications that solutions can be found. For example, some pharmaceutical firms, such as GlaxoSmithKline and Gilead, have recently made licensing arrangements with generic-drug manufacturers such as Aspen. The Food and Drug Administration has approved, under PEPFAR, several generic antiretroviral preparations for purchase and use outside the United States. Imaginative strategies focused on the long term will be needed if we are to fulfill our obligations, and solutions will require brand-name and generic pharmaceuticals to coexist

and prosper. Good economic policy, in this instance, can mean equally good public health policy.

The world currently has a perfect opportunity to further stimulate ongoing efforts by governments, the World Health Organization, and nongovernmental organizations to ensure the sustainability of HIV-treatment programs. Ambassador Randall Tobias, U.S. Global AIDS Coordinator and formerly a chief executive in the pharmaceutical industry, was recently elected chair of the Policy and Strategy Committee of the Global Fund. With leadership responsibilities for both PEPFAR and the Global Fund, Ambassador Tobias is in a unique position to bring stakeholders together to search for common ground and sustainable new policy directions. Such an initiative should be warmly received by all who are committed to finding a long-term solution.

Currently, only 11 percent of persons in sub-Saharan Africa who need antiretroviral therapy are receiving it. Ensuring that HIV-care initiatives continue to take root globally is not only a moral imperative, but a political and economic necessity as well.

An interview with Dr. Havlir can be heard at www.nejm.org.

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