enue, and as with the tax on tobacco, it could become a key tool in efforts to improve health.

No potential conflict of interest relevant to this article was reported.

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GLOBAL HEALTH

Rationing Antiretroviral Therapy in Africa — Treating Too Few, Too Late

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Related article, p. 1815

The past 6 years have seen striking advances in access to antiretroviral therapy in Africa. From 2002 onward, the international drive to scale up antiretroviral treatment gained considerable momentum, most notably with the establishment of the Global Fund to Fight AIDS, Tuberculosis, and Malaria, the "3 by 5" Initiative of the World Health Organization (WHO), and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Today, an estimated 3 million people in the developing world are receiving antiretroviral therapy.

The momentum has now begun to wane, with various groups arguing that the focus on AIDS has had its day and that health care funding should now be redirected to other areas, such as maternal and child health and primary care. But before the international community gives up on prioritizing care for patients with HIV infection, we believe that on-the-ground discussions must address not only whether enough has been done to scale up treatment but also whether the treatment that patients are receiving is good enough.

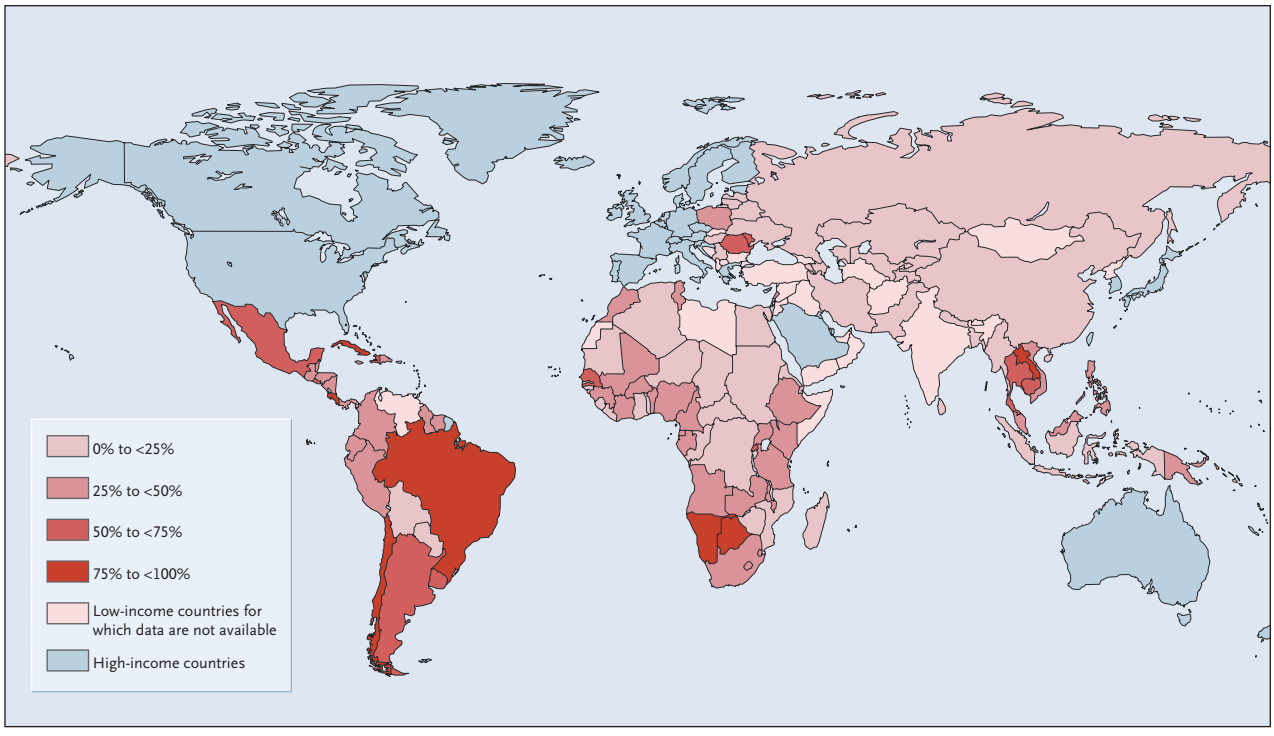
The standard approach to HIV treatment in Africa is to wait until people are visibly sick, treat them with effective but poorly tolerated drugs, and then wait until they are sick again before switching regimens. There are several problems with this approach.

The first is that too few people are receiving treatment. The 3 million people receiving antiretroviral therapy are usually said to account for about 30% of the need for such treatment, but even this rate reflects the use of stringent eligibility criteria that have been abandoned in wealthier countries.

Second, we are waiting until people are symptomatic before they are treated. In most African countries, patients begin receiving treatment when the CD4+ count falls below 200 cells per cubic millimeter, at which point most patients already have symptomatic and severe (WHO stage 3 or 4) infection. In the United States and Europe, treatment is initiated earlier — as soon as the CD4+ count reaches 350 cells per cubic millimeter — and increasingly, experts are arguing that even that is too late.

In many patients in Africa, the CD4+ count takes only about a year to decline from the cutoff for such early initiation to that for the later initiation now practiced in developing countries.[1] Although delaying therapy may mean saving money on drugs during this period, the long-term cost of such delays is increased substantially by the need for more intensive clinical care, decreased income, and likely regimen switches. Cost is thus no longer a tenable justification for delaying therapy. More important, recent observational data presented by Kitahata et al. in this issue of the *Journal* (pages 1815–1826) show that the risk of death increases by 69% when the initiation of therapy is delayed until the CD4+ count drops below 350 cells per cubic millimeter. Patients' immunologic nadir — how low their CD4+ count is allowed to drop — is predictive of the degree of benefit they will

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Estimated Proportion of Persons with HIV Infection Receiving Antiretroviral Therapy in Low-Income and Middle-Income Countries as of December 2007.
No coverage proportion was calculated for countries in which the estimated number of persons requiring therapy was less than 500. Data are from the World Health Organization.

obtain from future antiretroviral therapy. Although guidelines for low-income settings recommend initiating treatment when a patient's CD4+ count drops below 200 cells per cubic millimeter, patients frequently begin receiving therapy even later, on average when the CD4+ count is just over 100 cells per cubic millimeter. Enrolling patients in treatment programs earlier is a priority.[2]

An interactive map is available at NEJM.org

There are also important public health costs. For one thing, a policy of late initiation encourages the spread of tuberculosis. One recent study estimated that patients starting antiretroviral therapy at a CD4+ count below 200 cells per cubic millimeter have more than three times the risk of tuberculosis of those who begin therapy earlier.[3] Moreover, late initiation compromises the potential effect of antiretroviral therapy on HIV transmission by allowing patients to remain viremic longer. One study estimated that starting treatment earlier would reduce HIV transmission by 56%.[4] However, if the current guidelines for the initiation of therapy in the West were adopted in developing countries, several million more people would be eligible for care, and the treatment gap would widen even further.

Another concern is that in most developing countries, patients are receiving drugs with major tolerability issues. The majority of treatment programs in Africa use an antiretroviral regimen based on stavudine. There are a number of sound reasons for using this drug, including the fact that it forms part of a simple, affordable, fixed-dose combination. However, the drug's severe side effects have rendered it all but obsolete in the West. A tenofovir-based regimen would be preferable, but the use of tenofovir has largely been limited by its cost.

Furthermore, not only should initial treatment begin earlier in developing countries, but when the first-line regimen fails, patients should also be switched earlier to another regimen. In the Western world, evaluations of viral load and genotyping are performed regularly, and the drug regimen is altered at the first sign of virologic resistance. In Africa, access to viral-load assessment is extremely limited, and patients must wait until immunologic or clinical deterioration is manifested before being switched to new drugs, which reduces future treatment options and increases the risk of transmission.

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It should be acknowledged that although there are outstanding clinical questions regarding the optimal time for initiating and switching treatments, the overriding rationale behind current guidelines for antiretroviral therapy is rationing — limiting the number of people who must be treated, providing the cheapest available drugs, and delaying shifts to more expensive drugs for as long as possible. But as other experts have argued, rationing on the basis of clinical criteria alone is an inherently flawed way of prioritizing the needs competing for scarce resources.[5]

The drive to scale up antiretroviral treatment in Africa has encouraged a public health approach that promotes reaching the greatest number of patients with the simplest, most affordable regimens. We would argue that treating people when they are less sick with drugs that are less toxic and providing a simple tool for monitoring adherence and detecting treatment failure would be entirely consistent with this approach and would improve access to care by facilitating the decentralization of services from the hospital level to the clinic. Newer, more potent drugs should be considered for inclusion in treatment guidelines, rather than being reserved for use in salvage regimens for a minority of patients in the West. The better the drug, the simpler the treatment, and the fewer treatment switches will be necessary. Viral-load monitoring should be expanded to reinforce adherence and ensure that treatment failure is detected as early as possible.

Taking this new approach will require a reorientation of the organization and support of HIV care programs. A policy of earlier initiation of therapy could help to streamline services that are currently overwhelmed, by prioritizing clinic care according to patients' health needs. Clinic services could be primarily used by patients who are clinically sick, whereas patients with stronger immunity could, after initial consultation, receive follow-up medication and care in the community. In this way, a policy of earlier initiation of therapy could help to streamline services that are already overwhelmed by the competing needs of patients with various levels of illness.

Earlier treatment and regimen switching would initially require additional investment by national governments and the international community (in particular, PEPFAR and the Global Fund), but it might well turn out to be cheaper in the long run, as the need for managing clinical complications is reduced and the rate of new infections falls. The initial provision of antiretroviral therapy in the late 1990s ultimately led to massive cost savings, thanks to the avoidance of hospitalizations and opportunistic infections; in this way, Brazil alone is estimated to have saved more than $1 billion in 4 years. At the same time, increased demand forced the cost of medicines down considerably, from more than $10,000 per patient per year to less than $100. The same dynamic can be expected for a policy of early starting and switching, provided that there are clear messages to manufacturers and ministries of health to support expanded access to better drugs and diagnostics.

The battle to start providing antiretroviral therapy in the developing world has been won. The battle to provide the best care we can is just beginning.

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The opinions expressed in this article are those of the authors and do not necessarily represent those of Médecins sans Frontières, the University of Cape Town, the University of Ottawa, or Geneva University Hospital.

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