

# Rolling Out Antiretrovirals in Africa: There Are Still Challenges Ahead

R. Colebunders,<sup>1,2,3</sup> A. Ronald,<sup>1,2,4</sup> E. Katabira,<sup>1,2</sup> and M. Sande<sup>1,2,5</sup>

<sup>1</sup>Infectious Diseases Institute, Makerere University, and <sup>2</sup>Academic Alliance for AIDS Care and Prevention in Africa, Kampala, Uganda; <sup>3</sup>Institute of Tropical Medicine and University of Antwerp, Antwerp, Belgium; <sup>4</sup>University of Manitoba, Winnipeg, Canada; and <sup>5</sup>School of Medicine, University of Utah, Salt Lake City

(See the article by Akileswaran et al. on pages 376–85)

In their article “Lessons Learned from Highly Active Antiretroviral Therapy in Africa,” Akileswaran et al. [1] review the effectiveness of HAART programs in Africa. They report positive health outcomes, including high levels of treatment adherence and virological suppression that are comparable to those of industrialized countries [1]. Most of these studies, however, were performed in settings with significant external financial support, and the duration of patient follow-up was relatively short. Also, many of the studies are only currently available as abstracts, and as a result, a critical analysis of the strengths and weaknesses of the various programs is not possible. There is no doubt that the availability of antiretroviral drugs in Africa from the President’s Emergency Plan for AIDS Relief; the Global Fund for AIDS, Tuberculosis, and Malaria; and other donor programs is an extremely important life-saving initiative, especially when it is strategically linked to well-organized, community-based HIV-preven-

tion programs. However, the challenge to roll out antiretrovirals in Africa to all those who need them and to obtain achievable long-term results is daunting. In this commentary, we detail some of these challenges.

## WHEN TO START ANTIRETROVIRAL TREATMENT?

In most African countries, antiretroviral treatment is started for patients who have World Health Organization (WHO) stage III or IV disease or a CD4<sup>+</sup> lymphocyte count of <200 cells/ $\mu$ L [2]. At our Infectious Diseases Institute clinic at Makerere University and Mulago Hospital in Kampala, Uganda, the mean CD4<sup>+</sup> lymphocyte count at the start of antiretroviral therapy was 63 cells/ $\mu$ L for patients who started therapy during the last 6 months. Most of these patients received a diagnosis of HIV infection only when they presented to the hospital with a life-threatening opportunistic infection (OI). Waiting to start HAART until patients have such a low CD4<sup>+</sup> lymphocyte count is far from optimal. Multiple studies have now shown that full immune reconstitution and survival rates are reduced if antiretroviral therapy is started when CD4<sup>+</sup> lymphocyte counts are severely depressed [3]. Unfortunately, <10% of HIV-infected individuals in Africa are believed to know their

HIV status, and for the immediate future, most individuals will be present for care only when they develop life-threatening, AIDS-defining illnesses.

## HOW TO EXCLUDE OIs BEFORE COMMENCEMENT OF ANTIRETROVIRAL THERAPY?

In symptomatic patients, OIs should be diagnosed and treated before HAART is started. In most HIV treatment centers, the facilities to diagnose OIs are limited. We recently visited a hospital in Africa that was preparing for the roll-out of antiretrovirals and that was unable to perform a direct sputum smear examination to diagnose tuberculosis. Diagnostic and therapeutic capabilities for common OIs (particularly tuberculosis and cryptococcal meningitis) must be available in these centers if the life-saving potential of antiretrovirals is to be realized.

## HOW TO START?

A nonnucleoside reverse-transcriptase inhibitor (NNRTI) combined with a double-nucleoside reverse-transcriptase inhibitor (NRTI) backbone (i.e., coformulated, generic, fixed-dose combinations of stavudine, lamivudine, and nevirapine given twice per day) is currently the cheapest and simplest regimen for treatment of HIV infection and, as a result, is the most

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Reprints or correspondence: Dr. A. Ronald, Section of Infectious Diseases, St. Boniface General Hospital, 409 Tache Ave., Rm. C5124, Winnipeg, Manitoba R2H 2A6, Canada (aronald@ms.umanitoba.ca).

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widely used regimen in Africa. Zidovudine may be prescribed in place of stavudine at almost the same cost. These regimens were chosen for 74% of the patients in the Akleswaran review [1].

### **PROBLEMS WITH THE FIRST LINE REGIMENS: NNRTIS**

Nevirapine has an unpredictable hepatic metabolism, a very long pharmacokinetic tail after discontinuation, and a low genetic barrier to resistance. Starting a fixed-dose regimen of combination NNRTI-NRTI treatment without a reduced “lead in” dose of nevirapine for 2 weeks may be associated with increased toxicity, whereas stopping use of the fixed-dose combination without continuing the NRTIs for an additional 5–7 days may lead to NNRTI resistance [4]. Neither option is possible with fixed-dose combinations, but alternate strategies are often not available. Moreover, concern about the use of NNRTIs as first-line antiretroviral treatment is growing because of the increased use of nevirapine monotherapy to prevent mother-to-child transmission of HIV infection [5–7]. The risk of developing resistance after receipt of only a single dose of nevirapine has been estimated to be 32% [5, 6]. A study from Thailand suggested that, in women who develop drug resistance because of nevirapine prophylaxis, a first-line treatment regimen that contains an NNRTI will be considerably less effective [7]. Also, regimens that contain efavirenz should not be used by women at risk of pregnancy because of the teratogenic potential for the fetus [8]. Because of drug interactions with rifampin, the use of nevirapine is generally avoided in patients who require tuberculosis and antiretroviral treatment [9].

### **PROBLEMS WITH THE NRTI BACKBONE**

The fixed-dose combination of stavudine, lamivudine, and nevirapine is currently the least expensive regimen by far, and patients who pay for medication often are unable to alter therapy even if they develop

adverse effects. This often leads to severe, irreversible polyneuritis. This complication occurs frequently in patients with AIDS in Africa [10], probably because patients start receiving therapy when they have advanced HIV disease and because other risk factors that can induce peripheral neuropathy (e.g., malnutrition, vitamin B deficiency, and the use of other neurotoxic drugs, such as isoniazid) are often present [11]. On the other hand, an antiretroviral regimen that contains zidovudine may also not be optimal, because many patients with AIDS in Africa present with severe anemia, and transfusion facilities are not always available [12]. Indeed, we have witnessed patients dying of anemia in the months after starting a zidovudine-containing HAART regimen. Stavudine—and, less frequently, zidovudine—also may cause lipoatrophy and life-threatening lactic acidosis [13].

### **POSTEXPOSURE PROPHYLAXIS**

When only the generic, fixed-dose combination with nevirapine is available, this regimen is sometimes prescribed for post-exposure prophylaxis. This is dangerous, because nevirapine has been shown to cause life-threatening hepatotoxicity in healthy persons with high CD4<sup>+</sup> lymphocyte counts, particularly women [14–16].

### **ALTERNATIVE FIRST-LINE REGIMENS**

Because of the problems associated with NNRTI-containing regimens, an alternative first-line treatment regimen is needed. The combination of zidovudine, lamivudine (or emtricitabine), and tenofovir could be a welcome option. Two studies exploring the use of tenofovir plus zidovudine and lamivudine in antiretroviral-naïve individuals—one a pilot study from France [17], the other the large Ugandan-Zimbabwean Development of Antiretroviral Therapies [DART] trial [18]—observed response rates that were considered, at the recent 12th Conference on Retroviruses and Opportunistic In-

fections in Boston, to be satisfactory. Although subjects had a median baseline CD4<sup>+</sup> lymphocyte count of 100 cells/ $\mu$ L and a median viral load of 290,000 copies/mL, 61% of DART study participants achieved viral loads of <50 copies/mL at week 24, as determined by on-treatment analysis [18]. Without information about adherence to treatment and long-term efficacy data, however, it is certainly too early to recommend this regimen for large-scale use in Africa. Moreover, in the DART study, 21% of subjects developed anemia, which was severe (grade 4 or 5) in 5.5% of the cohort [19].

### **HOW TO MONITOR EFFICACY AND ADVERSE EFFECTS?**

Monitoring the efficacy of antiretroviral treatment in countries with limited resources is problematic because of the lack of available, inexpensive, and reliable laboratory facilities to perform viral load and resistance testing. Akleswaran and colleagues state that, for the moment, “a number of new techniques are available to provide cost-efficient alternatives, including total lymphocyte count, complete blood cell count, and clinical monitoring only” [1, p. 383]. The value of these methods remains to be established. To identify treatment failure early, we will need to develop and validate algorithms using clinical, adherence-based, and simple laboratory parameters. Until these methods are validated, CD4<sup>+</sup> lymphocyte counts remain the standard for monitoring care.

### **WHEN TO SWITCH?**

Today, because viral load and even CD4<sup>+</sup> lymphocyte counts may not be accessible, doctors may be reluctant to switch therapy for patients, even if clinical failure is presumably occurring and a second-line regimen is available. The current WHO clinical definition for treatment failure is the occurrence of a new WHO stage IV disease [2]. This criterion usually will portend a “late switch,” occurring after both virological and immunological failure and after the virus is likely to have developed

resistance to all 3 drugs in the first-line regimen.

## WHICH SECOND-LINE REGIMEN?

Second-line antiretroviral regimens are often in limited supply and may not be ideal in resource-restricted regions. Lopinavir-ritonavir, didanosine, and a thymidine analogue that was not used in first-line treatment is the regimen most frequently available. The thymidine analogue may have no antiretroviral activity because of previously developed cross-resistance. Adverse effects are common, and lopinavir-ritonavir needs to be kept refrigerated [20]. Therefore, additional second-line regimens are needed.

## ORGANIZATIONAL CHALLENGES

With the increased availability of antiretrovirals, HIV treatment clinics are being overwhelmed by patients. More patients are requesting HIV tests, and routine HIV testing is now being offered to hospitalized patients. Facilities and the necessary human resources to deal with large numbers of HIV-infected patients requiring care are currently lacking in most areas [21]. To cope with the increasing demand for antiretrovirals and the limited numbers of doctors in Africa, nurses, dispensers, clinical pharmacists, and counsellors must be organized into effective clinical teams for providing HIV care services. This will require major training initiatives, as well as reorganization of health services. The Academic Alliance for AIDS Care and Prevention in Africa, with its Infectious Disease Institute in Kampala, Uganda, is one such effort committed to this task.

## THE CRITICAL NEED FOR ONGOING MONITORING AND EVALUATION OF THE ANTIRETROVIRAL ROLL-OUT IN AFRICA

Observational studies, such as those compiled by Akleswaran et al. [1], are of value

as strategies are developed to rapidly expand antiretroviral access in Africa. However, prospective, well-designed studies are also essential if this massive public health effort by the global community is to be a credible, science-based endeavor. The roll-out of antiretrovirals must be carefully monitored and evaluated; the efficacy of different antiretroviral regimens, adherence to treatment, adverse effects, and patient morbidity and mortality all must be assessed in real time, to identify problems early and to institute corrective measures. Much of this information could be obtained through cohort studies and their ongoing analysis. Such cohort studies could not only be useful for comparisons of efficacies and adverse effects of different HAART regimens, but also to compare different systems of rolling out antiretrovirals. Rapid emergence of NNRTI resistance could derail the entire effort. Randomized, clinical trials need to be conducted in Africa in a manner similar to the approach taken in the West. The international community, multilateral organizations, and local governments should realize that, without an evidence-based plan to “scale up” HAART, there is a great risk that we will choose treatment regimens that are not optimal, leading ultimately to program failure and possibly widespread donor disillusionment.

## CONCLUSIONS

Since the “3 by 5” initiative was launched in 2003 by the WHO and UNAIDS, substantial progress has been rapidly made to increase the access to antiretrovirals to the millions of Africans who need treatment. But there are still major challenges that must be addressed to ensure that treatment is administered safely and effectively and is based on evidence from African data. The programs also must be rolled out with fiscal transparency and continuing urgency and accompanied by a secure drug logistical system. Widespread access to antiretrovirals, if consistently linked to prevention and if sustain-

able and well managed, has the potential to save generations of African citizens and their societies from decimation by this lethal virus.

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