The Extraordinary Hope of Antiretroviral Therapy in South Africa (Even for Patients with Tuberculosis or Kaposi Sarcoma!)

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(See the article by Cassol et al., on pages 324–32.)

The article “Therapeutic response of HIV-1 subtype C in African patients coinfected with either Mycobacterium tuberculosis or human herpesvirus–8” in this issue of the Journal of Infectious Diseases [1] demonstrates that outstanding virologic and immunologic responses to triple combination antiretroviral therapy (ART) occur in South African patients. These observations provide important insight into the feasibility of treating HIV-infected persons in resource-limited settings.

HIV and AIDS treatment in North America and Europe was revolutionized by the use of triple combination ART, which resulted in dramatic decreases in morbidity and mortality [2]. As the potency, adverse effects, and ease of ART administration continue to improve, HIV is becoming more and more manageable within the developed world. The hallmark of triple combination ART has been profound suppression of viral load to undetectable levels (<400 copies/mL) with increases in CD4+ cell counts. Moreover, ART has uniformly translated to improved health for HIV-infected persons by decreasing the risk of AIDS-related complications and death, as well as by decreasing the overall cost of medical care.

Unfortunately, the benefits of ART have been slow to arrive in the developing world, particularly in sub-Saharan Africa, which bears a disproportionate burden of the HIV/AIDS epidemic [3]. As ART has percolated slowly into the developing world, 2 myths have been propagated. The first myth is that the benefits of ART observed in developed areas of the world cannot be replicated in resource-poor settings. This myth gave rise to many arguments that have been made to discourage the introduction of this extraordinary, life-saving therapy in the areas of the world that need it the most. The past 12 months have provided an array of studies, including the study by Cassol et al. in this issue of the Journal [1], that have shattered this myth. The Cassol et al. study [1] and studies conducted in Cameroon [4], southern India [5, 6], and southern Africa [7] have demonstrated dramatically the positive impact of triple combination ART in the developing world. HIV-1 subtype C appears to respond no differently to ART than does subtype B. Adherence in resource-poor settings (when access is guaranteed) is excellent [8]—often better than in North American or European patients. These studies have also shown that the active ingredients in the most commonly used generic ARTs are comparable to “brand name” ART medications [9, 10].

The second myth is that patients in the developing world will be too ill with far-progressed opportunistic infections (OIs) to benefit from ART. The study by Cassol et al. in this issue of the Journal addresses the use of ART for the treatment of HIV in persons who have clinical manifestations of coinfection with Mycobacterium tuberculosis or human herpesvirus–8 (HHV-8). Coinfection with M. tuberculosis and HHV-8 are common in the developing world—in sub-Saharan Africa, in particular—and manifestations of these coinfections (tuberculosis [TB] and Kaposi sarcoma [KS], respectively) could complicate application of ART in these areas of the world. HIV-infected patients in the developing world tend to present with HIV very late during the course of the disease, usually with active OIs. TB is, by far, the most common OI. TB leads to significant nutritional wasting and will cause both specific and nonspecific activation in the immune system, which might lead to an increase in viral load [11] and further impair both HIV suppression
and immunologic recovery. Some clinicians have wondered whether patients with active TB or KS would be “just too sick” to benefit from triple combination ART or whether combination therapies for both HIV and these OIs would be too complex and impossible to manage effectively. Effective therapy for either TB or KS in the setting of triple combination ART may involve taking anywhere from 5 to 10 medications at any one time. The study by Cassol et al. demonstrates that patients with either of these active OIs respond well to triple combination ART utilizing a nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based regimen.

Although the study by Cassol et al. is small, it is well done, and the results provide important insight into the short-term antiviral effects of ART in a resource-limited setting. After 90 days of therapy, almost 94% of patients with active TB had undetectable viral loads (<40 copies/mL). Eighty percent of patients with KS had undetectable viral loads by 90 days. Patients with TB had slightly greater decreases in viral load, but this is probably because the baseline viral load in patients with TB was higher than that in patients with KS. The phase I decay of virus, which occurs within the first 7 days, was rapid and comparable to the decay observed in studies in the developed world. The phase II decay was slower and more gradual, consistent with that found in previous studies of HIV treatment. Despite the generalized immune activation that can occur with TB, which almost certainly has some impact on HIV replication, triple combination ART in this setting was enormously effective. It is important to note that, in the Cassol et al. study, patients with active TB were treated with 600 mg of efavirenz. Recent studies from Thailand have indicated that responses among patients in that country who were treated with rifampicin and 600 mg of efavirenz may be adequate [12]. These findings suggest that the pharmacokinetic interaction between efavirenz and rifampicin observed in populations in developed countries does not significantly impact the antiviral response of efavirenz-based therapy in resource-limited settings. The increased CD4⁺ cell count in patients with active TB was relatively greater than that in patients with KS, possibly because patients with TB have a larger, more dynamic population of highly productive CD4⁺ cells. For both cohorts, the increase in CD4⁺ cell counts was greatest during the first 7 days of treatment, a finding consistent with those from studies of HIV therapy in the developed world. These findings, together with other studies, strongly suggest that treatment of HIV-1 subtype C results in significant virologic and immunologic benefit, even in the setting of active OIs and low CD4⁺ cell counts. The long-term effects of ART in the resource-limited setting will need to be confirmed by continued follow-up of the patients in the Cassol et al. study and by other ongoing studies. Further research is needed on predictors and effective strategies to manage immune reconstitution syndrome in patients with OIs, particularly TB, who have begun receiving ART.

There are hosts of unanswered questions regarding HIV therapy in the developing world that must be addressed by research. How will response to ART in resource-limited settings be affected by differences in human genetics, culture, diet, and comorbidities? Will the extraordinary successes of treatment and outstanding suppression of viral load by triple combination ART with an NNRTI be durable over 1, 2, 5, or even 10 years [13]? In a setting in which access is highly challenging and patients may be starting and stopping treatment, will NNRTI resistance develop quickly, and will NNRTI-resistant virus be transmitted, leading to primary resistant HIV infection? What are the best and least expensive second-line regimens? Will patients, once they achieve dramatic improvement of their health, continue to be committed to treatment? Other, larger issues regarding broad-scale implementation of ART must be addressed, including the tremendous needs in health-care infrastructure, education and training of health care professionals in the areas of HIV and AIDS [14], low-cost monitoring of therapy [15–17], the introduction of new technologies, and secondary prevention to reduce new infections. The study by Cassol et al., along with many others that have appeared within the past 12 months, clearly demonstrates that triple combination ART is extraordinarily effective and practical in resource-limited settings, even in patients with low CD4⁺ cell counts and active OIs. Broad-scale implementation of this life-saving treatment must be widely supported not just by medical communities but also by governments, industry, and philanthropic groups worldwide. As treatment is implemented, an aggressive research agenda must be pursued in parallel, to determine how best to deliver ART, sustain it, and prevent new HIV infections worldwide, as well as improve the lives of those already infected.

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