Choice of an Initial Antiretroviral Regimen in the Resource-Limited Setting: The Cost of Virologic Failure

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(See the article by Gupta et al. on pages 712–22)

Tremendous strides have been made in the provision of antiretroviral therapy to people in areas of the world with the most critical need, and these efforts have had a positive impact on the health of persons living with HIV/AIDS. A recent report from the World Health Organization (WHO) estimates that 700,000 people initiated antiretroviral treatment in 2006 and that, by the end of 2006, 2,015,000 people living with HIV/AIDS were receiving antiretroviral treatment in low- and middle-income countries around the world [1]. The WHO report estimates that, during a 3-year period, the number of people receiving antiretroviral treatment in sub-Saharan Africa increased 13-fold, from 100,000 in 2003 to >1.3 million in 2006. In Botswana, where 95% of people who needed antiretroviral therapy had access to it by the end of 2006, a 20% reduction in adult mortality was observed between 2004 and 2005 [2]. Worldwide, expanded access to antiretroviral treatment is estimated to have prevented 250,000–350,000 AIDS-related deaths during 2003–2005 [3]. If these successes continue, the rapid scale-up in the worldwide provision of antiretroviral therapy over the past 5 years will undoubtedly be viewed by future generations as one of the major public health accomplishments of the 21st century.

Expanded access to antiretroviral treatment has its costs. Obviously there are the monetary costs of providing antiretroviral drugs, clinical care, and laboratory monitoring of toxicities and efficacy. But there is also a virologic cost of treatment failure. A cross-sectional analysis of the antiretroviral scale-up program in Malawi [4] found virologic failure in 13% of patients—a prevalence of virologic failure that is consistent with first antiretroviral regimen failure rates in resource-rich settings. The surprising finding in Malawi was the high rate of antiretroviral drug-resistance mutations among persons who had experienced virologic failure: 76% of virus isolates recovered from patients for whom treatment had failed had the M184V mutation, which is associated with resistance to the nucleoside reverse-transcriptase inhibitors (NRTIs) lamivudine and emtricitabine; 94% had mutations associated with resistance to the non-NRTIs (NNRTIs) nevirapine and efavirenz. High rates of antiretroviral drug resistance were also observed in a recent analysis of antiretroviral resistance at the time of first regimen failure in the KwaZulu-Natal province of South Africa, where the prevalence of M184V/I mutations and NNRTI resistance were 64% and 78%, respectively [5]. If these rates of virologic failure and antiretroviral resistance are representative of those in other settings, then upwards of 240,000 people are infected with antiretroviral drug-resistant HIV-1 worldwide. With time and continued antiretroviral treatment, the prevalence of acquired drug resistance will likely continue to increase in resource-limited settings, where viable second- and third-line antiretroviral regimens are not readily available. Of even greater concern is that the dissemination of drug-resistant virus in resource-limited areas could impact the efficacy of initial antiretroviral regimens in the future.

In this issue of Clinical Infectious Diseases, Gupta et al. [6] provide a comprehensive review of the patterns of antiretroviral drug resistance that are detected at the time of failure of an initial antiretroviral regimen. Gupta and colleagues performed a meta-analysis to compare the incidence and patterns of antiretroviral drug resistance at the time of virologic failure of an initial antiretroviral regimen composed of 2 NRTIs plus either an NNRTI or a ritonavir-boosted protease inhibitor (bPI). In total, 7275 participants who were receiving an initial antiretroviral regimen through participation in 1 of 20 different clinical trials were analyzed: 3063 received a regimen including a bPI, and
4212 received a regimen including an NNRTI. Importantly, all participants included in this analysis received either lamivudine or emtricitabine as one of the NRTIs. Although there was no significant difference in the rates of virologic failure for recipients of the NNRTI-based and bPI-based regimens, there were significantly higher rates of genotypic antiretroviral drug resistance among persons for whom the initial NNRTI-containing regimen failed. These findings are consistent with a previous systematic review of the consequences of initial antiretroviral regimen failure by Bartlett et al. [7], who reported that antiretroviral regimens that include a bPI had lower resistance costs at the time of virologic failure than did NNRTI-based regimens. An important finding of Gupta et al. [6] is that recipients of NNRTI-based regimens also had higher rates of lamivudine or emtricitabine resistance and multinucleoside resistance than did recipients of bPI-based regimens. Thus, Gupta and colleagues added to our current knowledge about the resistance consequences of initial treatment regimen failure by conducting a focused systematic comparison of NNRTI-based versus bPI-based regimens, with a data set large enough to compare the rates of resistance to specific drugs or classes of drugs.

Gupta et al. [6] conclude that their findings are of "particular significance for the developing world" (p. 712), because the rates of resistance to NRTIs and NNRTIs are much higher in these parts of the world. They further suggest that bPI-containing regimens may be more appropriate for resource-limited settings because of erratic drug supply and long periods spent receiving a failing regimen. Current WHO guidelines for the use of antiretrovirals in resource-limited settings [8] recommend use of an NNRTI initially and reservation of protease inhibitors (PIs) for second-line therapy. The rationale for the WHO recommendation is that use of a PI in an initial treatment regimen "essentially rules out second-line options in the setting of limited formularies within a public health approach: no potent or durable regimens have been identified for recommendation following initial PI failure in this situation" (p. 26).

Are the findings of Gupta et al. [6] sufficient to justify a call for wider use of bPIs in initial antiretroviral regimens in resource-limited settings? To answer this question, a number of factors must be weighed in the balance. As Gupta and colleagues point out, the frequency and type of antiretroviral drug resistance at the time of initial regimen failure is only one of the factors to consider; comorbidities, regimen convenience, potential adverse drug effects and interactions with other medications, and cost must also be considered when individualizing antiretroviral regimen selection. Cost, in particular, weighs heavily against routine use of a bPI-containing regimen in resource-limited settings. For instance, in sub-Saharan Africa, the mean cost of branded coformulated lopinavir-ritonavir is $514 per year, and the cost of generic indinavir plus ritonavir is $554 per year, not including other components of the regimen [9]. Thus, the cost of bPIs alone—even generic versions—is still many-fold higher than the cost of an entire 3-drug NNRTI-based regimen.

Other limitations of the study by Gupta et al. [6] should be considered carefully before these findings are generalized to the resource-limited setting. First, the cases of antiretroviral failure analyzed by Gupta and colleagues involved participants in clinical trials conducted largely in developed countries. Because of frequent monitoring of the plasma HIV RNA level, virologic failure in these clinical trial participants was detected much earlier than would be expected in a resource-limited setting where viral load testing is less accessible. Although there is less antiretroviral resistance early in the course of treatment failure when a bPI-based regimen is used, we do not know what the prevalence of antiretroviral resistance—particularly that associated with the M184V/I mutation—is at later time points during the course of bPI-based regimen failure. The clinical trials participants included in the Gupta and colleagues’ analysis also come from regions of the world where HIV-1 subtype B is prevalent, and different patterns of antiretroviral drug resistance mutations have been observed in other HIV-1 subtypes [10–12]. We do not know whether HIV-1 subtype affects the temporal appearance of antiretroviral drug–resistance mutations during the course of treatment failure in bPI- versus NNRTI-based regimens. Finally, although Gupta and colleagues infer that failure of a bPI-based initial antiretroviral regimen is easier to treat because of less acquisition of drug resistance, this study does not provide information on second-line regimen success in the study population. Evidence that the success of a second regimen is greater if a bPI is used in the initial regimen in a resource-limited setting is needed before one can make a strong argument for wider use of bPIs in initial antiretroviral regimens in resource-limited settings.

Despite the greater risk of antiretroviral drug resistance at the time of virologic failure, NNRTI-based regimens are still the mainstay of antiretroviral treatment in the resource-limited setting. Rather than begin treatment with a bPI-based regimen, perhaps a first step to curb the evolution of antiretroviral resistance in resource-limited settings is to implement the tools needed for early detection of virologic failure, as argued recently by Smith and Schooley [13].

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