

# Highly Active Antiretroviral Therapy (HAART)—Plus: Next Steps to Enhance HAART in Resource-Limited Areas?

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(See the article by Ramadhani et al. on pages 1492–8)

HAART has been extremely successful in suppressing HIV infection, restoring immune function, and improving health, and it has led to dramatic decreases in morbidity and mortality in those areas of the developing world where HIV infection is most prevalent. Studies from the ART in Lower Income Countries cohort and from Malawi, Uganda, Cote d'Ivoire, and India have clearly demonstrated that >75% of HIV-infected individuals who receive fixed-dose combination (FDC) therapy with a nonnucleoside reverse-transcriptase inhibitor have excellent viral suppression [1–5]. These successes have been outstanding and have driven the scale-up of HAART as a global health priority. More than 2 million individuals in the developing world are receiving HAART; most of these individuals are in sub-Saharan Africa, which bears the brunt of the HIV epidemic.

The successful development of HIV care programs to deliver HAART faces

daunting challenges. Now that it has been clearly demonstrated that HAART is an enormous success in saving lives and improving health, it is time to move to the next step. Who is not benefiting from HAART? Which patients are experiencing treatment failure? What interventions can be integrated into HIV care to more effectively provide HAART in resource-poor areas? Are these interventions feasible and sustainable? A hint to many of these answers can be found in tuberculosis care. Directly observed therapy (DOT) is commonly misconstrued as only providing combination tuberculosis therapy. The DOT strategy is a 5-point plan that emphasizes governmental commitment to care and treatment, access to diagnostic procedures, uninterrupted drug supply chains, DOT for adherence monitoring during critical phases of treatment, and monitoring and re-evaluation of program management and outcomes. The DOT portion of this strategy emphasizes more than “pill watching,” because it involves social engagement and case management, with referral for associated problems and issues. DOT-plus programs have further demonstrated an ability to successfully treat multidrug-resistant tuberculosis successfully with a comprehensive program in resource-poor areas, as well.

The article by Ramadhani et al. [6] in this issue of *Clinical Infectious Diseases* explores predictors of incomplete adherence and virologic failure among 150 patients who have been receiving FDC therapy and HAART for >6 months. Disclosure of HIV infection status to an individual other than a health care provider was strongly protective against virologic failure (adjusted OR, 0.10;  $P = .04$ ), whereas self-funded treatment (adjusted OR, 23.5;  $P = .04$ ) and the need to sacrifice health care for other necessities (adjusted OR, 19.8;  $P \leq .01$ ) were associated with maladherence [6].

These findings indicate how HIV care programs can be augmented. The protective role of disclosure of HIV infection status to persons other than health care providers was dramatic. The authors speculate that this may be the result of multiple factors, including adherence support, less social stigma, reduced social isolation, and potentially reduced depression [6]. Trying to dissect the positive impact of disclosure of HIV infection status to family or supportive members in the community is extremely difficult. However, other models of care have also shown tremendous benefit associated with social support by community health workers or family members. The “*accompagnneur*” model of HIV

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care support pioneered by Dr. Paul Farmer successfully uses such a program. However, this model is resource intensive; therefore, it is difficult to apply it to programs that care for tens of thousands of patients. Of note, only 5% of the patients described in Ramadhani et al. [6] did not disclose their HIV infection status to individuals other than their health care providers. A more cost-effective model may include specialized interventions, such as the assignment of “accompagneurs” or “adherence buddies” focused on those patients who have been proven to have difficulty with disclosure of their HIV infection status.

The study by Ramadhani et al. [6] clearly demonstrates that interruptions in nonnucleoside reverse-transcriptase inhibitor-based HAART regimens may lead to increased rates of virologic failure and antiretroviral-resistant infection [6]. It is often assumed that interruptions in HAART are attributable to poor adherence, which is under the control of the patient. However, this study [6] demonstrates that treatment interruptions may frequently be attributable to factors beyond patient control, such as the high cost of medication relative to earned income; the difficulty of accessing health care services in areas with poor roads, poor transportation services, and scarce health care facilities; or challenges involving distribution, with resultant interrupted delivery of drug supplies [6]. The recently published companion study from Uganda by Oyugi et al. [7] demonstrates that treatment interruptions are often the result of disruptions in drug supply that are outside of the control of either an individual patient or an individual clinic. For example, in one country, confusion between customs authorities and the National Drug Authority prevented clearance of FDC HAART, which, in turn, resulted in a nationwide drug shortage [7]. These findings emphasize the pivotal role of development in the management of HIV infection in resource-limited countries.

Within the ART in Lower Income

Countries cohort, access to free HAART, as well as to free medical care, was associated with significant improvement in survival [1]. The study by Ramadhani et al. [6] demonstrates that a longer duration of self-funded therapy led to poorer adherence and a trend toward the development of antiviral drug resistance. In sub-Saharan Africa, this implies that the availability of free long-term HAART, as well as structural changes to ensure adequate delivery of treatment, remain critical but fragile factors in managing the HIV infection epidemic. International funding institutions, such as the Global Fund, President’s Emergency Plan for AIDS Relief, and the Clinton Foundation, must place priority on monitoring supply chain issues and ongoing access to FDC HAART combinations. Ongoing funding should take into account the political and institutional will of each country to provide ongoing access to HAART.

Ramadhani et al. [6] also found that incomplete adherence to HAART was associated with sacrificing health care for other necessities, such as food, clothing, childrens’ school fees, or housing (OR, 20.7;  $P < .01$ ). Similarly, Byakika-Tusiime et al. [8] found that HAART interruptions were associated with competing family financial demands, such as childrens’ school fees and the costs of relatives funerals. These findings pose the greatest challenges for the delivery of effective care for HIV-infected individuals in resource-poor countries. Poverty remains a critical and essential barrier to accessing health care. Free medications may be useless if food is not available. Breaking the chain of disease and poverty by providing for continued education and family support is key.

The task of providing additional support or employment to HIV-infected patients to ensure that the financial demands of everyday life are met (thereby preventing HAART interruptions) is extremely challenging, but it is not impossible. Programs centered in resource-limited areas are beginning to acknowledge that HIV

infection management must include not only the delivery of drugs but also nutritional, economic, and psychosocial support. In western Kenya, examples of such programs operate under the umbrella of the Academic Model for the Prevention and Treatment of HIV/AIDS (AMPATH) and include their Nutritional Support Programs and Family Preservation Initiative [9]. Across the AMPATH system of 19 clinics, rates of food insecurity range from 20% to 50% of patients. In 2002, the HAART and Harvest Initiative was launched when a 10-acre farm was donated to AMPATH. The Appropriate Grassroots Initiative, a British nongovernmental organization, designed this program to provide food security for a minimum of 6 months to patients and their families. Since the establishment of the HAART and Harvest Initiative, the farms have become training centers for sustainable, locally acceptable farming techniques, as well as centers for HIV education and community outreach. Five additional farms have subsequently been established, bringing the total number of farms, at present, to 6 [9]. In 2005, the US Agency for International Development and the World Food Program became partners in the effort to supply nutrition to AMPATH patients, allowing for the addition of maize, beans, oil, and maize or soy flour to the fresh vegetables, eggs, and yogurt provided by the HAART and Harvest Initiative farms. At present, AMPATH provides food supplementation to 28,000 patients and family members.

Because food supplementation in the short term does not address the long-term issues of poverty and economic dependency, AMPATH also started the Family Preservation Initiative, which is an economic development program designed to assist patients in developing skills to allow them to become economically independent [9]. The services of the Family Preservation Initiative include counseling, business training courses (in conjunction with the US Peace Corps), on-site business consultation, microfinance and microsav-

ings, a craft workshop, occupational skills development, a food cooperative, and transitional housing [9]. To date, ~3000 patients have benefited from this program. Such holistic approaches, which recognize the needs of families that have been impacted by HIV infection or AIDS and provide the tools needed to overcome poverty and achieve economic independence, may be effective in sustaining antiretroviral adherence over time.

Within the past 2 years, multiple programs in Asia and Africa have demonstrated that FDC HAART has been enormously successful in controlling HIV infection and has led to substantial benefits in health. The challenge, as we move forward, is to identify key barriers to long-term successful treatment with HAART. A HAART-plus approach not only allows programs to think “outside the box” and consider issues as wide ranging, for example, as individualized treatment interventions with an “accompagnneur” for at-risk patients, but also allows for consideration of structural changes to im-

prove drug procurement and distribution practices that stabilize supply chain management. In addition, programs should explore innovative responses to the challenges posed by extreme poverty through family-centered nutrition and educational support, such as those programs that have been developed by AMPATH in western Kenya. A HAART-plus approach that supports the family as well as the patient will lead to improved health, as well as to improved health care delivery systems.

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