Antiretroviral Therapy in Resource-Poor Settings

Decreasing Barriers to Access and Promoting Adherence

Joia S. Mukherjee, MD, MPH, Louise Ivers, MD, MPH, DTMH,* Fernet Leandre, MD,† Paul Farmer, MD, PhD,* and Heidi Behforouz, MD**

Summary: Since 2002, the HIV Equity Initiative of the nongovernmental organization Partners in Health has been expanded in conjunction with the Haitian MOH to cover 7 public clinics. More than 8000 HIV-positive persons, 2300 of whom are on antiretroviral therapy (ART) are now followed. This article describes the interventions to promote access to care and adherence to ART developed in reference to the specific context of poverty in rural Haiti. User fees for clinic attendance have been waived for all patients with HIV and tuberculosis and for women presenting for prenatal services. Additionally, HIV testing has been integrated into the provision of primary care services to increase HIV case finding among those presenting to clinic because of illness, rather than solely focusing on those who present for voluntary counseling and testing (VCT). Once a patient is diagnosed with HIV, medications and monitoring tests are provided free of charge and transportation costs for follow-up appointments are covered to defray patients' out-of-pocket expenses. Patients are given home-based adherence support from a network of health workers who provide psychosocial support and directly observed therapy. In addition, the neediest patients receive nutritional support. Following the description of the program is an approximation of the costs of these interventions and a discussion of their impact.

Key Words: adherence, antiretroviral therapy, community health workers, nutrition, resource-poor settings, user fees

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Adherence to antiretroviral therapy (ART) delays the progression to AIDS[1,2] and the development of antiretroviral resistance.[3] Much of the medical literature on adherence to ART is focused on measuring the individual patient's ability to take ART as prescribed.[4] The underlying assumption in much of this body of work is that once the medicines are prescribed, the patient has regular and reliable access to the clinic and the medications. Because some of the risk factors for nonadherence described in North American studies, such as active drug use, are more common in poor populations,[5] when ART was introduced in resource-poor settings, there was fear that adherence would be a major problem and promote widespread resistance to ART.[6,7] However, studies in developing countries have shown comparable or better levels of individual adherence than what is seen in North American and European populations.[8,9] Resource-limited settings, however, present unique challenges to ART adherence. A multitude of structural barriers prevent access to health care and the regular supply of antiretroviral drugs. These include the cost of medical care, drugs, lack of integration of HIV testing with primary health care, tuberculosis, STI and women's health services, and the difficulty on making follow-up appointments during the long distances, family responsibilities, and the prohibitive cost of transportation. These factors affect the patient's ability to take medications as prescribed by the health care provider.

This article discusses the interplay between access and adherence in resource-poor settings and, based on our work in rural Haiti with poor communities, outlines strategies to decrease barriers to access and to increase adherence to ART. Finally, based on our experience, we estimate the costs of implementing these access and adherence support strategies in resource-poor settings.

PROGRAM DESCRIPTION

Since 1998, the nongovernmental organization (NGO) Partners in Health (PIH) has been providing ART to people through a charity hospital, the Clinique Bon Sauveur, in Haiti's Central Department under the HIV Equity Initiative (HEI). In 2002, the initiative was expanded into the public clinics in collaboration with the Haitian Ministry of Health (MSPP) and now covers 7 public clinics, following more than 8000 HIV-positive persons, 2300 of whom are on ART. Most of the people served by the clinics are poor subsistence farmers or have been migrant workers in urban Port-au-Prince or the plantations of the Dominican Republic. The prevalence of HIV is 5% among people attending the general clinics and 2% among pregnant women. The lessons learned from the early phase of the HEI was that the context of poverty factors such as lack of access to transport, food insecurity, and user fees for medical care, posed more significant barriers to adhering to long-term therapy than a patient's individual behavior. Several critical components were put into place to decrease these

From the *Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and †Zanmi Lasante, Cange, Haiti.

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Reprints: Joia Mukherjee, MD, MPH, Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital, Harvard Medical School, 641 Huntington Avenue, Boston, MA 02115 (e-mail: jmukherjee@pih.org).

barriers. First, all services and medications are provided free of charge to the patient. It has been documented by several projects that user fees are a significant barrier to seeking HIV testing, obtaining laboratory evaluations, and attending follow-up appointments.[10] Such cost sharing is detrimental to long-term adherence, as data from Senegal[11] and Botswana[9] indicate. In the HEI, user fees for services (visits and monitoring) and all medications are waived entirely. All treatment is given free of charge (including not only ART but drugs for opportunistic infections, family planning, and medications for other conditions such as hypertension).

Second, HIV testing, treatment, and care are provided in the context of primary care services. This is particularly important and primary care clinics were revitalized by providing essential medicines and paying stipends to MSPP staff in rural areas where patients routinely walk 4 or more hours to seek care. Most of the people attending the PIH/MSPP clinics come only when they are ill rather than to seek testing for HIV per se. In the context of primary health care, ill patients are screened for tuberculosis, treatable causes of diarrheal disease, sexually transmitted diseases, and other conditions that may be associated with HIV. As part of the evaluation of the ill patient, HIV testing may be offered by the clinician, if indicated. This strategy, sometimes called "opt out" or "routine offer" HIV testing, has been found to be acceptable in many settings, particularly when ART is available.[12,13]

The third aspect of the program to increase access and adherence to HIV treatment is an attempt to minimize the significant out-of-pocket expenses. Studies from several settings have shown that costs such as payment for transportation to and from a clinic serve as a deterrent to ART adherence. Patients attending PIH/MSPP clinic receive a monthly transportation stipend to attend follow-up appointments. Transportation for emergency visits is also covered by the program.[14] Similarly, a lack of food has been associated with poor adherence to ART, and provision of food and micronutrients has been shown to improve outcomes[15–17] Many families throughout the developing world spend more than 50% of their household income on food, and food production and wage earning are adversely affected when an adult has AIDS.[18,19] Therefore, the PIH/MSPP program provides food or cash transfers for food to the most vulnerable patients.

The fourth aspect of the HEI program to support adherence and minimize barriers to access is the use of community health workers. Community health workers perform active case finding for HIV and tuberculosis and provide a link between the patient, family, community, and clinic. Their daily role is to give psychologic support and directly observed therapy to HIV patients requiring ART. The development and activities of these workers have been described in detail elsewhere.[20,21]

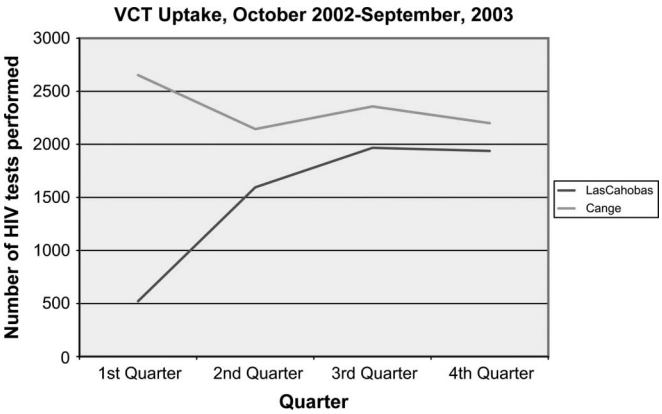

FIGURE 1. VCT uptake with introduction of HIV–primary health care integration: Lascahobas versus Cange. (*From* Walton D, Farmer P, Lambert W, et al. Integrated HIV prevention and care strengthens primary health care: lessons from rural Haiti. *J Public Health Policy*. 2004;25:137–158; with permission.)

RESULTS

The Zamni Lasante proposal written to the Global Fund to Fight AIDS, Tuberculosis, and Malaria and, later, the President's Emergency Plan for AIDS Relief included the staffing and essential medications that would be needed to increase the provision of primary health services that would be expected for the population at each site. The improvement in general health services, done with money for HIV scale-up, served to markedly increase the utilization of primary health care. With this context, we presumed the uptake of HIV testing would increase.

To discern whether or not the packages of interventions described previously (discontinuing user fees, integrating HIV testing with primary health care, and providing transport fees and other material assistance to patients) increased the overall uptake of HIV testing and the use of health care services, records were analyzed from the Lascahobas MSPP clinic from the beginning of the integrated PIH/MSPP program in October 2002 through the end of 2003. The results of that analysis, which have been published elsewhere,[22] are seen in Figure 1. The number of VCT sessions at Lascahobas increased dramatically after initiation of the program and compares favorably with the rates reported from the referral center in

TABLE 1. Use of Services After the HIV–Primary Health Care Integrated Model of Care Was Implemented

Public Clinic	July 2002, Before MSPP–Zanmi Lasante Community Partnership Average No. Ambulatory Visits per Day	December 2003, After Initiation of MSPP–Zanmi Lasante Community Partnership Average No. Ambulatory Visits per Day
Lascahobas	20	400
Belledere	10	150
Thomonde	10	250
Boucan Carre	10	250

TABLE 2. Approximate Costs of Adherence and Access Interventions in the PIH/MSPP HEI

Intervention	Cost ($US) per Patient per Year	Description
Waiving user fees	$6	Monthly visits to clinic, normal user fee $0.05 per month × 12 months
Ancillary tests and monitoring	$20	Yearly CD4 cell count, radiographs, hemoglobin, liver function tests
Transportation fees for monthly clinic visit	$60	Monthly transport fee $5 per month × 12 months
Community health worker	$100	Community health worker paid $500 per year for coverage of 5 patients
Total	$186	

Cange Clinique, Bon Sauveur, where HIV VCT and full primary health care services have been available since 1986.

With this series of interventions, 40,000 HIV tests were performed in 2005. 2300 patients are on ART. Of the 1500 patients who have been on ART for more than 1 year, fewer than 100 have died or had clinical or immunologic failure that required a change to second-line ART, suggesting excellent adherence to ART and medical follow-up. Virologic monitoring has not yet been performed in this population because of logistic and financial barriers.

Although there are many facets to the HEI adherence and access interventions, some of the costs can be estimated. Table 2 outlines the cost of the various interventions. The transportation fee averages $60 US per patient per year. The cost of waiving the MSPP user fee for 12 monthly visits is $6 US per patient per year. The cost of waiving the cost for ancillary tests (including a yearly CD4 cell count, radiographs, and routine laboratory monitoring tests) is approximately $20 US per year. This standard package adds up to approximately $86 US per year per patient. Community health workers are paid approximately $500 US per year and follow, on average, 5 patients, adding a cost of $100 US per patient per year. The total cost of the adherence package is $186 US per year.

Patients who have severe wasting and children with HIV who have signs of malnutrition receive nutritional support. We estimate that the cost of food for the patients who are economically and nutritionally the neediest is approximately $450 US per year. This intervention is currently being evaluated in partnership with the World Food Program.

DISCUSSION

Scale-up of HIV testing and treatment cannot be done without improving access to primary health care and integrating HIV services with that context. Moreover, adherence programs in resource-poor settings must work to improve access to health care.

The low rate of treatment failure, indicated by few deaths and few patients needing to change to second-line ART, suggests that adherence to medical follow-up and antiretroviral medication is excellent in the HEI. Monitoring of virologic response and for the development of resistance within the cohort of patients on ART is planned for this year. Additional work is planned to focus on measuring the impact and cost of individual interventions on clinic attendance and adherence. A first-line nevirapine-based generic antiretroviral regimen costs approximately $150 US per person per year. Our basic package of support costs approximately $186 US. Investments in adherence, if effective, should yield a return in the form of a delay in the need for second-line ART. Second-line antiretroviral medications, typically lopinivir/ritonovir, tenofovir, and abacavir, are not available as generic drugs and cost approximately $1500 US per patient per year. Thus, each year the need for a second-line regimen is delayed, $13,000 US is saved in antiretroviral costs. Additionally, patients are more likely to remain healthy and out of the hospital if resistance is delayed.

In the United States, where adherence support is not universal, approximately 50% of patients on a new antiretroviral regimen develop a detectable viral load (the precursor of resistance) at the end of 1 year,[23] but little has been done to provide financial support for adherence programs.

The challenge of administering long-term therapy in settings of extreme privation is significant. Although adherence to ART is much discussed in the public health arena, little has been done to advocate for financial support of initiatives that have been shown to improve adherence. HIV program should be rooted in sole primary health care to benefit a greater proportion of the community. HIV diagnosis, treatment, and monitoring should be provided free of charge in poor communities to ensure that drugs are taken properly and not shared with family members or sold. Additionally, with the millions of dollars being invested in the scale-up of ART, a lack of food security in the most heavily HIV-burdened countries threatens HIV programs and the health and survival of the most vulnerable.

REFERENCES

1. de Olalla PG, Knobel H, Carmona A, et al. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2002;30:105–110.
2. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS*. 2001;15:1–2.
3. Bangsberg D, Hecht F, Charlebois E, et al. Adherence to protease inhibitors, HIV-1 viral load and development of drug resistance in an indigent population. *AIDS*. 2000;14:357–366.
4. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Ann Intern Med*. 1999;131:81–87.
5. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity and applications. *J Clin Epi*. 1997;50:105–116.
6. Harries AD, Nyangulu DS, Hargreaves NJ, et al. Preventing antiretroviral anarchy in Africa. *Lancet*. 2001;358:410–414.
7. Frater AJ, Dunn DT, Beardall AJ, et al. Comparative response of African HIV-1 infected individuals to highly active antiretroviral therapy. *AIDS*. 2002;16:1139–1146.
8. Orrell C, Bangsberg DR, Badri M, et al. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS*. 2003;17:1369–1375.

9. Weiser S, Wolfe W, Bangsberg D, et al. Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana. *J Acquir Immune Defic Syndr*. 2003;34:281–288.
10. Russell S. The economic burden of illness for households in development countries: a review of the studies focusing on malaria, tuberculosis and HIV/AIDS. *Am J Trop Med Hyg*. 2004;71(Suppl 2):147–155.
11. Laniece I, Ciss M, Desclaux A, et al. Adherence to HAART and its principal determinants in a cohort of Senegalese adults. *AIDS*. 2003;17 (Suppl 3):S103–S108.
12. Centers for Disease Control. Introduction of routine HIV testing in prenatal care—Botswana, 2004. *MMWR Morb Mort Wkly Rpt*. 2004;53: 1083–1086.
13. Westheimer EF, Urassa W, Msamanga G, et al. Acceptance of HIV testing among pregnant women in Dar-es-Salaam, Tanzania. *J Acquir Immune Defic Syndr*. 2004;37:1197–1205.
14. Rowe KA, Makhubele B, Hargreaves JR, et al. Adherence to TB preventive therapy for HIV-positive patients in rural South Africa: implications for antiretroviral delivery in resource-poor settings? *Int J Tuberc Lung Dis*. 2005;9:263–269.
15. Ndekha MJ, Manary MJ, Ashorn P, et al. Home-based therapy with ready-to-use therapeutic food is of benefit to malnourished, HIV-infected Malawian children. *Acta Paediatr*. 2005;94:222–225.
16. Villamor E, Saathoff E, Manji K, et al. Vitamin supplements, socioeconomic status, and morbidity events as predictors of wasting in HIV-infected women from Tanzania. *Am J Clin Nutr*. 2005;82: 857–865.
17. Fawzi WW, Msamanga GI, Spiegelman D, et al. A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med*. 2004;351:23–32.
18. Rutengwe RM. Identifying strategic interventions for improving household food and nutrition security in an urban informal settlement, South Africa. *Asia Pac J Clin Nutr*. 2004;13(Suppl): S169.
19. Smith Fawzi MC, Lambert W, Singler JM, et al. Factors associated with forced sex among women in rural Haiti: implications for the prevention of HIV and other STDs. *Soc Sci Med*. 2005;60:679–689.
20. Farmer P, Léandre F, Mukherjee JS, et al. Community-based approaches to HIV treatment in resource-poor settings. *Lancet*. 2001; 358:404–409.
21. Farmer P, Léandre F, Mukherjee JS, et al. Community-based approaches to the treatment of advanced HIV disease, introducing DOT-HAART. *Bull World Health Organ*. 2001;79:1145–1151.
22. Walton D, Farmer P, Lambert W, et al. Integrated HIV prevention and care strengthens primary health care: lessons from rural Haiti. *J Public Health Policy*. 2004;25:137–158.
23. Gross R, Bilker WB, Friedman HM, et al. Effect of adherence to newly initiated antiretroviral therapy on plasma viral load. *AIDS*. 2001;15: 2109–2111.