HIV Antiretroviral Therapy in Resource-limited Settings: Experiences from Haiti

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An unprecedented international effort to expand high activity antiretroviral therapy (HAART) to resource-poor nations has been launched. The World Health Organization (WHO) has created antiretroviral (ARV) treatment guidelines adapted to resource-poor settings. The first-line regimen is two nucleoside reverse transcriptase inhibitors (NsRTIs) and one nonnucleoside reverse transcriptase inhibitor (NNRTI). Therapy is initiated by clinical staging and CD4 T-cell counts when available. Adherence is the responsibility of health care workers. The use of ARV therapy in resource-poor settings faces several challenges, including the poverty of patients, political and social upheavals and violence, social stigma associated with HIV/AIDS, unreliable pharmacy systems, tuberculosis, and lack of trained health care workers. Using our experience in Haiti, we describe how we have addressed these challenges with the goal of increasing access to care for the poor with HIV/AIDS.

Introduction

The first published description of AIDS in a resource-poor nation was from Haiti in 1983 [1]. It is now recognized that greater than 90% of the approximately 40 million people with HIV/AIDS in the world live in resource-poor settings [2•].

Since the first report of AIDS two decades ago [3], a causative agent has been isolated and HIV antiretroviral (ARV) agents discovered, moving wealthy nations into the era of highly active ARV therapy (HAART) [4–8]. Unfortunately, medicine did not move as quickly in resource-poor settings. At the end of 2004, 700,000 of the 5.8 million people between the ages of 15 to 49 who need ARV therapy are receiving it, a 12% coverage rate [9]. Although seemingly low, this rate reflects an unprecedented international effort to expand HAART to resource-poor nations.

This paper reviews significant milestones in the expansion of HAART in resource-poor settings, current treatment guidelines for HAART and the unique challenges to the provision of ARVs in these settings, and our experience addressing these challenges in Haiti.

Antiretroviral Scale-up in Resource-limited Nations: Significant Milestones

In 1996, HAART became standard of care in the United States after a study showed that two nucleoside reverse transcriptase inhibitors (NsRTIs) in combination with a single protease inhibitor (PI) decreased mortality by almost 50% at the end of 24 weeks [6,10].

In the late 1990s, countries such as Brazil, Thailand, Senegal, and Uganda attracted international attention by creating government-sponsored programs on HIV prevention and ARV treatment [11,12•,13–15]. Smaller pilot programs in Cote D'Ivoire and Haiti also provided comprehensive HIV care with ARVs [16,17]. Still, the majority of affected countries had no access to ARVs. Barriers to making HIV prevention and care a priority were attributed to the cost of ARVs, lack of infrastructure, stigma of admitting HIV was a problem, and even total disbelief in the causative agent of AIDS [18].

In 2001, the United Nations Secretary General Kofi Annan issued a "call to action" to create a fund consisting of governmental, public, and private donors that would be able to "make a sustainable and significant contribution to the reduction of infections, illness and death, thereby mitigating the impact caused by HIV/AIDS, tuberculosis, and malaria…"[19]. By December 2004, 860 million US dollars had been disbursed by the Global Fund Against AIDS, Tuberculosis, and Malaria (GFATM), with Haiti being one of the first countries to receive an award.

In May 2003, President George W. Bush signed a US 15 billion dollar, 5-year initiative, called the President's Emergency Plan for AIDS Relief (PEPFAR), to fund the promotion of HIV testing, the supporting of abstinence-based peer education, the training of medical personnel, the purchasing of equipment for clinics and laboratories, and the

Table 1. World Health Organization (WHO) recommendations for initiating antiretroviral therapy in adults and adolescents with documented HIV infection

If CD4 testing available
WHO stage IV disease irrespective of CD4 cell count
WHO stage III disease (including but not restricted to HIV wasting, chronic diarrhea of unknown etiology, prolonged fever of unknown etiology, pulmonary tuberculosis, recurrent invasive bacterial infections, or recurrent/persistent mucosal candidiasis) with consideration of using CD4 cell counts less than 350/mm^3 to assist decision making*
WHO stage I or II disease with CD4 cell counts less than or equal to 200/mm^3†
If CD4 Testing unavailable
WHO stage IV disease irrespective of total lymphocyte count
WHO stage III disease (including but not restricted to HIV wasting, chronic diarrhea of unknown etiology, prolonged fever of unknown etiology, pulmonary tuberculosis, recurrent invasive bacterial infections, or recurrent/persistent mucosal candidiasis), irrespective of total lymphocyte count
WHO stage II disease with a total lymphocyte count less than or equal to 1200/mm^3‡

*CD4 count advisable to assist with determining need for immediate therapy. For example, pulmonary TB may occur at any CD4 level and other conditions may be mimicked by non-HIV etiologies (eg, chronic diarrhea, prolonged fever).
†The precise CD4 level above 200/mm^3 at which antiretroviral treatment should start has not been established.
‡A total lymphocyte count of less than or equal to 1200/mm^3 can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms (stage II or III) exist. It is not useful in the asymptomatic patient. In the absence of CD4 cell testing, asymptomatic HIV-infected patients (WHO stage I) should not be treated because there is currently no other reliable marker available in severely resource-constrained settings.
Adapted from World Health Organization [22•].

purchasing of low-cost ARV treatments [20]. The program focuses on 15 of the world's hardest hit countries, which hold 50% of the world's HIV infections. PEPFAR also provides technical assistance and capacity building to support national AIDS programs through the Centers For Disease Control Global AIDS Program (CDC-GAP) and the United States Aid for Interagency Development (USAID).

In September 2003, at the United Nations General Assembly High Level Meeting on HIV/AIDS, the leaders of the World Heath Organization (WHO), the Joint United Nations Program on HIV/AIDS (UNAIDS), and the GFATM declared that lack of access to HIV treatment was "a global health emergency." The plan to provide ARV therapy to at least three million people by 2005 (the "3 by 5" plan) was presented on World AIDS Day, December 1, 2003 [21].

Antiretroviral Treatment Guidelines for Resource-poor Settings

The WHO created guidelines initially in 2002 and then revised them in 2003 [22•]. The guidelines take into account the weak health care infrastructure, low laboratory capacity, and a low doctor/patient ratio present in many resource-poor settings. The document promotes clinical guidelines for staging patients' progression from HIV to AIDS, and promotes the use of these clinical guidelines as criteria to start and monitor patients on ARV therapy—this is in contrast to the standard criteria for CD4 and HIV viral load used in resource-rich countries [23] (Table 1).

The first-line regimen recommended by the WHO is two NsRTIs plus one NNRTI. The drugs recommended are zidovudine (AZT) or stavudine (d4T) with lamivudine (3TC) plus either nevirapine (NVP) or efavirenz (EFV) (Fig. 1). Factors in favor of a NNRTI-containing first-line regimen are its ease of administration, efficacy, and lack of a refrigeration requirement.

The choice of the three drugs used in the first-line regimen is generally made on a national or regional level, based on access, cost, and side-effect profiles in local patient populations. The choice between AZT and D4T depends on the prevalence of anemia, which prohibits AZT use. The choice between EFV or NVP is dependent on cost and the side effect profiles, especially in women. EFV has the advantage that it has a long halflife, allowing once-a-day dosing, and can be used concomitantly with rifampin, facilitating HIV and tuberculosis cotreatment. However, EFV should not be used in women of childbearing potential because of risk of teratogenicity [24]. NVP also has important limitations in women. Studies have shown a 12-fold increased risk of hepatotoxicity in women with CD4 T-cell count greater than 250 cells/mm^3 [25]. A NNRTI with daily dosing, no teratogenicity, good side-effect profile in women, and no drug-drug interactions with tuberculosis medications is desperately needed for resource-poor settings, but unfortunately does not yet exist.

The second-line regimen currently recommended by the WHO is two new NsRTIs with a single PI. The PI is given instead of the NNRTI because of high cross-resistance between the two NNRTIs, Nevirapine and Efavirenz [26]. The second-line regimen consists of the NsRTIs abacavir (ABC) plus didanosine (ddI) or the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir (TDF) given with the PIs lopinavir or saquinavir [22•] (Fig. 1). Both PIs are given with small doses of ritonavir, a PI that inhibits the cytochrome P450 (CYP450) enzyme system and allows a twice daily dosing.

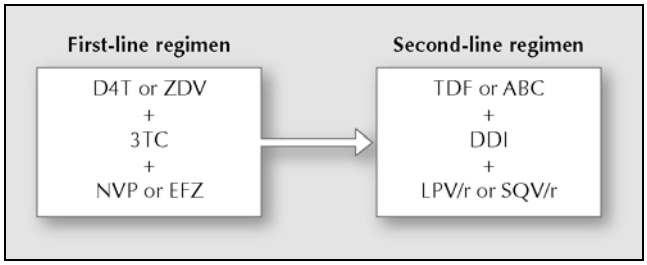

Figure 1. World Health Organization's first- and second-line antiretroviral regimens in resource-poor nations. Dose of didanosine (DDI) should be reduced from 400 mg to 250 mg when co-administered with tenofovir (TDF). Lopinavir/ritonavir (LPV/r) and saquinavir/ritonavir (SQV/r) require secure cold chain. NFV can be considered as an alternative in resource-limited settings without cold chain. ABC— abacavir; EFV—efavirenz; 3TC—lamivudine. *Adapted from* World Health Organization [22•].

Adherence and Resistance in Resource-poor Settings

For an ARV program to succeed in providing effective regimen without inducing HIV resistance, health care workers must assume responsibility for ARV adherence. Studies have shown that if a patient is on an ARV regimen that suppresses the HIV virus to undetectable levels and good adherence is maintained, the risk of virological failure is extremely unlikely [27]. A prospective study following a cohort on PI-containing regimens showed that patients who reported correctly taking more than 95% of their monthly doses over a median of 6 months had virologic failure rate of 22%. In this same group, no opportunistic infections or death occurred. In contrast, the group who reported less than 95% adherence had a virologic failure rate of 72%, with a 5% incidence of opportunistic infections, and 2% incidence of deaths [28].

ARV programs in resource-poor nations have shown that adherence rates comparable with those of the developed world are possible. Brazil started providing free access to ARVs in the 1990s. Now with 154,000 patients receiving ARV therapy in 2004, covering 86% of patients in need, Brazil has increased the survival time of patients living with HIV/AIDS from 6 months to 5 years [11,12•]. A cross-sectional analysis of 1972 patients taking ARVs showed that 75% of patients reported at least 95% adherence, similar to rates seen in the United States. Some notable predictors of nonadherence in this study were the use of a more complex drug regimen, drug regimens with a high number of pills, and patients with less than 2 years of formal education [29].

As barriers to adherence exist on multiple levels in resource-poor and resource-rich nations, adherence on a global scale is unlikely to reach 100%. Because of this, the WHO recommends that countries planning to implement ARV programs should implement a surveillance system so that each program can modify ARV treatment recommendations accordingly. In 2001, the WHO Global HIV Drug Resistance Surveillance Program was established to provide a unified method of monitoring resistance [22•].

Antiretroviral Scale-up in Haiti

Haiti is located on the western third of the Caribbean island of Hispanoila and has a population of 8 million people [30]. Haiti is the poorest country in the Western Hemisphere, with a per capita income of 380 dollars per year [31]. Haiti ranks 150th out of 175 countries on the United Nations Human Development Index [32]. The country has suffered near constant political and social unrest for the last 20 years [33]. The per capita total expenditure on health was 56 US dollars in 2001 [30]. The Pan American Health Organization (PAHO) estimated that only 60% of the Haitian population has access to health care services [34].

Haiti and HIV

Haiti has a generalized HIV epidemic, with approximately 5% of the adult population infected [30]. Haiti has the highest rates of HIV infection in the Americas and the highest rates anywhere outside of Africa [2•]. Recent national seroprevalence studies suggest that the prevalence rates of HIV in prenatal clinics declined from 5.2% to 3.4% between the years 2000 and 2004 [35]. Reasons for this decrease may be government support for AIDS activities, a solid partnership between government and private health sector, and specific interventions such as universal screening of blood products, educational campaigns, condom promotion, and widespread voluntary counseling and testing.

Haiti and Antiretrovirals

Despite many challenges, there are currently approximately 3500 patients on ARV therapy in Haiti, with an ARV coverage rate of 8% for 2004 [9]. The national goal is to achieve a 50% coverage rate within 5 years. At present, patients are primarily treated at the GHESKIO Center (Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes) in Port au Prince and at Partners in Health (PIH) in the rural Central Plateau.

In 1998, GHESKIO began to provide HAART to a small group of patients using donated drugs. This number expanded to 1800 with the availability of money from both the GFATM and PEPFAR. The ARV clinic promotes a multidisciplinary team approach using doctors, nurses, psychologists, social workers, pharmacists, laboratory technicians, and field workers. Therapy is monitored using CD4 counts done by the FACSCount System (Becton Dickinson, San Jose, CA). Viral loads are not done. Field workers have a key role, going into the community to seek patients who have missed their appointments. In the analysis of the first patients on ARV therapy, one-year mortality was 10%. This compares to a one-year mortality of 60% in natural history studies [36]. The mean CD4 count increase at one year was 180 cells/mm^3.

Partners in Health began offering HAART in 1997 using community health workers, or accompagnateurs, to

carry out a directly observed therapy model of care [16]. In 2004, PIH extended their comprehensive care sites throughout the Central Plateau, and now they are following approximately 1500 patients on ARVs [37; J. Mukherjee, personal communication].

Unique Challenges to Effective HAART in Resource-poor Settings: Examples from Haiti

Poverty

Poverty clearly affects the ability of patients to feed themselves. Past studies in Haiti and elsewhere suggest that malnutrition and micronutrient deficiency may affect HIV-disease progression [38]. Although the first-line regimen is not dependent on food for effective absorption, a common Haitian belief is that taking medications without food will cause further illness. Despite counseling, many patients still refuse to take pills on an empty stomach. GHESKIO supplies a ration of food to each patient on ARVs to address this issue. As the ARV scale-up process continues and the food demand becomes greater, this will continue to be a critical issue to address to prevent poor adherence and ARV resistance.

Poverty also affects the ability of patients to travel to clinic for regular follow up and medication refills. The cost of taxi fare to and from the clinic may be one day's wages for many patients. This is particularly difficult for those patients who have to travel great distances because the ARV expansion program has not yet reached their region. Some of these patients inevitably miss followup visits and therefore medication refills. GHESKIO now offers a travel reimbursement to all patients on ARV to address this problem. Partners in Health deliver medications to patients via their accompagnateur system. We anticipate that with more primary health care clinics providing HAART, travel distances and expenses for patients can be minimized.

Violence and insecurities

Insecurity because of the volatile social and political situation in Haiti affects ARV patients and staff. An empty patient waiting room in our Port au Prince clinic is often a harbinger of likely violence that day, as patients stay home when rumors of street protests circulate. Alternatively, patients may leave the capitol city altogether and go to more rural sites, which can overload the few ARV sites in the provinces [39]. During times of general insecurity, followup is difficult because of the lack of telephones and the inability to send field workers to areas of extreme danger. Other centers in Haiti have had hospital vehicles and property stolen during times of political violence [40].

To respond to this problem, GHESKIO has developed an emergency plan to continue care during times of general insecurity. A skeleton crew works at the main clinic, even during the worst violence. Healthcare staff who can visit patients at home or receive patients in their own home are designated in each city neighborhood. An emergency supply of medicine was purchased by GHESKIO and stored in sites throughout the city during the worst periods of violence. As many resource-poor nations have frequent social and political turmoil, such emergency care plans should be developed as part of a clinic's ARV program.

Stigma

HIV-related stigma is unfortunately common in Haiti [41]. In a national survey, 90% of respondents said that a HIV-seropositive person was obligated to disclose their status to others, but only 20% of the female respondents and 25% of the male respondents said that a seropositive person should be allowed to continue to work with others [42].

Stigma may prevent patients from accessing health care. In a survey of patients at GHESKIO, many reported being afraid to attend clinic lest members of the community learn that they have AIDS [43]. Patients with AIDS report being turned away by physicians at other clinics in Haiti because they are HIV-seropositive [44].

Successful ARV treatments have been shown to effectively lower the stigma in Haitian communities [45]. Conversely, decreased stigma may improve ARV care. In a study in Botswana [46], patients who were able to disclose their HIV status to a friend or family member approximately threefold more likely to be adherent. Therefore, we can hope for a benign circle: successful ARV programs will decrease stigma, and decreased stigma will facilitate care.

Unreliable pharmacy stock of antiretroviral

Despite the decreasing financial barriers to ARV access, nonfinancial challenges to a dependable pharmacy stock of ARVs exist in Haiti [47]. For example, in our clinic in Port au Prince, medications ordered from generic manufacturers arrive 4 to 12 months late. Once medications do arrive in country, delays of more than 6 weeks can occur at customs offices. The WHO advised our clinic to hold off using a large supply of generic medications that were delivered because of concerns about manufacturer quality control. These difficulties in maintaining a reliable pharmacy supply force doctors to make decisions about whether to do a "structured treatment interruption" or switch medications in order to maintain a suppressed viral load. In an analysis of patients treated at GHESKIO, 6% of patients required a change in medication due to rupture in pharmacy stock.

In response, the Haitian government is leading efforts with international agencies to develop a national pharmacy system to assure a reliable source of ARVs in Haiti. As other resource poor settings expand access to ARVs, a national pharmacy plan is a critical component of scaleup efforts.

Tuberculosis

In a natural history study out of Port au Prince, tuberculosis (TB) was both the most common presentation of symptomatic HIV disease and the most common AIDS-defining

Table 2. Antiretroviral therapy (ART) recommendations for individuals with tuberculosis disease and HIV co-infection

CD4 cell count	Recommended regimen	Comments
CD4 < 200/mm^3	Start TB treatment. Start ART when TB treatment is tolerated (between 2 wks and 2 mo)[*]: EFV-containing regimens[†‡§]	Recommend ART. EFV is contraindicated in pregnant women or women of childbearing potential without effective contraception
CD4 200–350/mm^3	Start TB treatment. Start one of the regimens below after the intitiation phase (start earlier if severly compromised): EFV-containing regimens[†] or NVP-containing regimens in case of rifampicin-free continuation phase TB treatment regimen	Consider ART
CD4 > 350/mm^3	Start TB treatment	Defer ART[¶]
CD4 not available	Start TB treatment	Consider ART[*††]

[*]Timing of ART initiation should be based on clinical judgement in relation to the other signs of immunodeficiency. For extrapulmonary TB, ART should be started as soon as TB treatment is tolerated, irrespective of CD4 cell count.
[†]Alternatives to the EFV portion of the regimen include: SQV/RTV (400/400 mg twice daily), SQV/r (1600/200 mg every day, sgc), LPV/RTV (400/400 mg twice daily) and ABC.
[‡]NVP (200 mg every day for 2 weeks followed by 200 mg twice daily) may be used in place of EFV in absense of other options. NVP-containing regimens include: d4T/3TC/NVP or ZDV/3TC/NVP.
[§]EFV-containing regimens include d4T/3TC/EFV and ZDV/3TC/EFV.
[¶]Unless non-TB stage IV conditions are present (Table 1). Otherwise start ART upon completion of TB treatment.
[††]If no other signs of immunodeficiency are present and patient is improving on TB treatment, ART should be started upon completion of TB treatment.
ABC—abacavir; EFV—efavirenz; LPV—lopinavir; NVP—nevirapine; RTV—ritonavir; SQV—saquinavir; TB—tuberculosis.
Data from World Health Organization [22•].

illness, with 39% of the cohort developing TB [36]. At our ARV clinic in Port au Prince, approximately 15% of patients started on ART are also on TB medications. The need to concurrently treat HIV and tuberculosis in Haiti presents challenges on many levels, including drug interactions, drug toxicities, and risks for decreased adherence with the high pill burden [48].

The optimal time to start ARV in the patients on TB treatment is not known. The WHO recommends that in patients with a CD4 count less than 200/mm^3 one should start TB therapy and then an efavirenz-containing ARV regimen after 2 weeks for up to 2 months if the ARV regimen is well-tolerated. Patients with a CD4 count between 200/mm^3 and 350/mm^3 should begin TB treatment and then ARV therapy after the induction period of TB treatment. For patients with a CD4 above 350/mm^3, physicians should treat the TB and defer ARVs until the patient meets criteria for therapy. In the event CD4 counts are not available, the WHO recommends to start ARV therapy along with TB therapy, using clinical judgment and signs of immunodeficiency to decide how quickly to initiate the ARV therapy [22•] (Table 2).

In patients who receive cotreatment, rifampin complicates ARV therapy because it is a strong inducer of the CYP450 system, which can reduce the NNRTI and/or PI levels in the blood to subtherapeutic levels. Although rifabutin can be used in its place giving less CYP450 induction, it is not widely available in resource-poor nations because of high costs. In patients receiving rifampin, EFV may be dose adjusted from 600 mg to 800 mg at bedtime [49]. In women of childbearing potential, who should not take EFV, a triple nucleoside regimen or a NVP-based regimen can be used with great caution, monitoring closely the liver function tests. The WHO also recommends ritonavir-boosted lopinavir and saquinavir as another alternative, although a recent US Food and Drug Administration (FDA) announcement reported increasing levels of hepatoxiticy in healthy volunteers on a boosted saquinavir/rifampin regimen [22•,50].

When treating TB and HIV concurrently, the provider may be faced with the immune reconstitution syndrome (IRS), an inflammatory syndrome, which has been observed at an incidence of 10% to 40 % of patients who have been started on TB and ARV agents concurrently [51,52]. Clinical symptoms include persistent or increasing fever, worsening pulmonary infiltrates, and lymphadenopathy. IRS is more likely to occur in patients with extrapulmonary TB, with a lower CD4 count and higher HIV viral load at baseline. IRS occurred at a median of 48 days in one study, with a greater increase in CD4 cell percentage (as opposed to CD4 cell count) being its main predictor [52]. In a resource-poor setting with limited laboratory capacity, the clinical management of a patient on ARVs with symptoms suggestive of IRS can be confusing. The differential diagnosis can be a therapeutic failure to TB medications, a new opportunistic infection, or a drug reaction, such as abacavir hypersensitivity.

The need for trained health care providers

There is a severe shortage of trained personnel in Haiti for expansion of HIV services nationally. The majority of doctors trained in Haiti leave to work outside of the country. Of the approximately 2000 doctors who stay, the majority have private practices in Port au Prince, leaving large

segments of rural Haiti to be cared for by foreign physicians and Haitian nurses. An evaluation performed on the 13 hospital centers selected to be ARV scale-up sites in Haiti showed staff needs at all levels, including clinicians, pharmacists, laboratory technicians, and counselors [53].

In order to produce competent ARV providers, the GHESKIO Center and PIH are providing intensive training and onsite supervision for doctors, nurses, pharmacists, laboratory technicians, and social workers. A national curriculum on the use of ARVs has been finalized. From months of May to December 2004, the ARV training team at GHESKIO trained 87 health care professionals from 13 institutions in the use of ARVs. The initial 3-week training consisted of didactics, small group case discussions, and hands-on experience in the clinic, laboratory, or pharmacy. Supervision and evaluation of the trainees occurs, with monthly onsite visits at each hospital center performed by a mobile team of GHESKIO providers. All participants are also invited to discuss cases or other problems with the GHESKIO training team by e-mail and instant messaging, using the internet technology installed in each hospital system Refresher courses on ARV treatment will occur every 6 months. By the year 2009, our objective is to train personnel in over 100 sites in order to fulfill the scaleup goal of 25,000 people on ARV therapy.

Conclusions

Increased support for resource-poor nations in the fight against HIV/AIDS finally arrived in the beginning of this millennium. The WHO has created ARV treatment guidelines that are adapted to resource-poor settings. Resource-poor nations such as Haiti have demonstrated the ability to use this support to successfully treat large numbers of patients with ARV, despite multiple challenges. The lessons learned from these experiences should be used to expand access to care, treat more poor AIDS patients, and achieve treatment coverage rates in resource-poor countries that are comparable to developed nations.

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