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## Antiretroviral Therapy in a Thousand Patients with AIDS in Haiti

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### ABSTRACT

#### BACKGROUND

The one-year survival rate of adults and children with the acquired immunodeficiency syndrome (AIDS), without antiretroviral therapy, has been about 30 percent in Haiti. Antiretroviral therapy has recently become available in Haiti and in other developing countries. Data on the efficacy of antiretroviral therapy in developing countries are limited. High rates of coinfection with tropical diseases and tuberculosis, along with malnutrition and limited laboratory monitoring of therapy, may decrease the efficacy of antiretroviral therapy in these countries.

#### METHODS

We studied the efficacy of antiretroviral therapy in the first 1004 consecutive patients with AIDS and without previous antiretroviral therapy who were treated beginning in March 2003 in Port-au-Prince, Haiti.

#### RESULTS

During a 14-month period, three-drug antiretroviral therapy was initiated in 1004 patients, including 94 children under 13 years of age. At enrollment, the median CD4 T-cell count in adults and adolescents was 131 per cubic millimeter (interquartile range, 55 to 211 per cubic millimeter); in children, a median of 13 percent of T cells were CD4-positive (interquartile range, 8 to 20 percent). According to a Kaplan–Meier survival analysis, 87 percent of adults and adolescents and 98 percent of children were alive one year after beginning treatment. In a subgroup of 100 adult and adolescent patients who were followed for 48 to 56 weeks, 76 patients had fewer than 400 copies of human immunodeficiency virus RNA per milliliter. In adults and adolescents, the median increase in the CD4 T-cell count from baseline to 12 months was 163 per cubic millimeter (interquartile range, 77 to 251 per cubic millimeter). In children, the median percentage of CD4 T cells rose from 13 percent at baseline to 26 percent (interquartile range, 22 to 36 percent) at 12 months. Treatment-limiting toxic effects occurred in 102 of the 910 adults and adolescents (11 percent) and 5 of the 94 children (5 percent).

#### CONCLUSIONS

This report documents the feasibility of effective antiretroviral therapy in a large number of patients in an impoverished country. Overall, the outcomes are similar to those in the United States. These results provide evidence in support of international efforts to make antiretroviral therapy available to patients with AIDS in developing countries.

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**A**NTIRETROVIRAL THERAPY WITH THREE or more medications is the international standard of care for patients with the acquired immunodeficiency syndrome (AIDS).<sup>1,2</sup> In developed countries, antiretroviral therapy decreases human immunodeficiency virus (HIV) viral load, increases the CD4 T-cell count, and dramatically improves survival.<sup>3-7</sup> However, 90 percent of the world's 40 million people with HIV infection or AIDS live in developing countries, where high rates of coinfection with tropical diseases, tuberculosis, and malnutrition, together with limited laboratory monitoring, may decrease the efficacy of antiretroviral therapy. Since treatment has only recently become available in developing countries, data on the effects of antiretroviral therapy in these settings are limited.<sup>8-12</sup>

We report the outcomes for the first 1000 patients with AIDS and without previous antiretroviral therapy who were treated consecutively at a clinic in Port-au-Prince, Haiti, beginning in March 2003, when international funding for antiretroviral therapy first became available.<sup>13</sup> Haiti is the poorest country in the Western Hemisphere and has suffered from nearly constant political unrest for the past 20 years.<sup>14</sup> AIDS was recognized in Haiti in the early 1980s.<sup>15</sup> HIV infection occurs primarily through heterosexual transmission, and the prevalence is currently estimated at 3 percent in the adult population.<sup>16,17</sup>

## METHODS

### PATIENTS

Since 1983, the clinic of the Haitian Study Group for Kaposi's Sarcoma and Opportunistic Infections (GHESKIO) has provided the Port-au-Prince population, which is currently estimated at about 2 million people, with free HIV counseling, testing for HIV infection, and services for prevention of HIV infection, as well as care for patients with AIDS.<sup>18</sup>

Between March 2003 and December 2004, the CD4 T-cell count was determined for all adult and adolescent patients coming to the GHESKIO clinic with symptoms of HIV infection. Antiretroviral therapy, according to World Health Organization (WHO) guidelines and without regard to the perceived likelihood that the patient would adhere to the therapy, was then initiated for patients with an AIDS-defining illness or a CD4 T-cell count under 200 per cubic millimeter.<sup>1,19</sup> The diagnosis of HIV infection in children was based on serologic test-

ing, clinical findings, and the percentage of T cells that were CD4-positive; antiretroviral therapy was initiated in infected children according to WHO pediatric guidelines.<sup>1</sup>

The full complement of personnel serving the cohort of 1004 patients described in this report consisted of five community health workers, two AIDS peer counselors, one social worker, one pharmacist, five nurses, and three physicians. The patients were routinely seen in the clinic by a physician every two weeks during the first three months of treatment and by a nurse monthly thereafter. Medications were dispensed directly to the patients on a monthly basis.

### TREATMENT

First- and second-line antiretroviral-therapy regimens followed WHO guidelines, as recommended by the Haitian government.<sup>1</sup> The first-line antiretroviral-therapy regimen for adults and adolescents consisted of zidovudine, lamivudine, and efavirenz. Single-drug substitutions were permitted: stavudine could be substituted for zidovudine, and nevirapine could be substituted for efavirenz. Other single-drug substitutions were permitted, according to WHO guidelines. The first-line regimen for children under 3 years of age substituted nevirapine for efavirenz.

WHO-approved generic medications constituted about 90 percent of the supply. When generic drugs were not available, brand-name medications were purchased. The cost of the three antiretroviral medications per patient per year ranged from \$550 for generic medications to \$750 for brand-name medications. We budgeted an additional \$1,000 per patient per year to cover other costs, including personnel (\$450), laboratory monitoring (\$300), medications other than antiretroviral drugs (\$75), data monitoring (\$75), and miscellaneous other costs (\$100). We estimated the overall cost per patient per year as about \$1,600.

Extrapulmonary tuberculosis, but not pulmonary tuberculosis, was considered an AIDS-defining illness.<sup>16</sup> HIV-infected adults and adolescents with pulmonary tuberculosis and a CD4 T-cell count of more than 200 per cubic millimeter were treated for tuberculosis, and initiation of antiretroviral therapy was deferred. In patients with tuberculosis who had a CD4 T-cell count between 50 and 200 per cubic millimeter, antiretroviral therapy was initiated after the completion of two months of tuberculosis therapy. In patients with a CD4 T-cell count of

less than 50 cells per cubic millimeter, tuberculosis treatment and antiretroviral therapy were started simultaneously. The tuberculosis regimen consisted of two months of isoniazid, rifampin, ethambutol, and pyrazinamide daily, followed by four months of isoniazid and rifampin daily.<sup>20</sup>

Adherence to therapy was encouraged by home visits, provision of free telephone cards for patients to call clinic staff, peer counseling by people with AIDS, pill counts, and social support programs. If it was indicated, patients were referred for nutritional aid, and counseling was offered to pregnant women, parents of HIV-infected children, and victims of domestic violence. Directly observed antiretroviral therapy, which has been very effective in rural Haiti,<sup>21</sup> was not feasible for our urban patients, who have limited social networks and frequently change their addresses.

#### CLINICAL MEASUREMENTS

Body weight was measured at every visit. The z score for weight for children was reported as the number of standard deviations above or below the median weight for age. Laboratory monitoring included the baseline CD4 T-cell count by flow cytometry (Becton Dickinson) and measurement of hemoglobin. The CD4 T-cell count was determined every six months. Follow-up hemoglobin measurements, liver-function tests, and serum chemical analyses were performed if clinically indicated. The level of HIV RNA in plasma at 12 months was determined in a subgroup of all available adult and adolescent patients who had been followed up for 48 to 56 weeks in December 2004. The Amplicor HIV-1 Monitor PCR Test (Roche), with a lower limit of detection of 400 copies of HIV RNA per milliliter, was used.

#### STATISTICAL ANALYSIS

The institutional review boards at GHESKIO and at Weill Medical College of Cornell University approved this study. We collected data from an electronic medical record and from the charts of patients with AIDS in whom three-drug antiretroviral therapy had been initiated between March 1, 2003, and April 30, 2004. Follow-up data collected through December 31, 2004, were included. The data were analyzed by an intention-to-treat approach with the use of SAS software. Proportions were compared by the chi-square test with Yates' correction or, for expected cell values of less than five, by Fisher's exact test. Means and medians were compared by Stu-

dent's t-test and the Wilcoxon rank-sum test, respectively. Kaplan–Meier survival analyses were used to estimate the time from the initiation of antiretroviral therapy to death and the time from initiation to the first treatment-limiting toxic drug effect. For patients who did not reach the end point, the data were censored at the date of the last visit. The log-rank test was used to compare survival times between strata. The Cox proportional-hazards model was used for multivariate analysis. Variables associated with mortality in previous publications or in our clinical experience were included in the initial model. Variables were removed from the model by a backward selection procedure if the value of alpha was greater than 0.05. Confounders causing a 10 percent change in another predictor were left in the model.

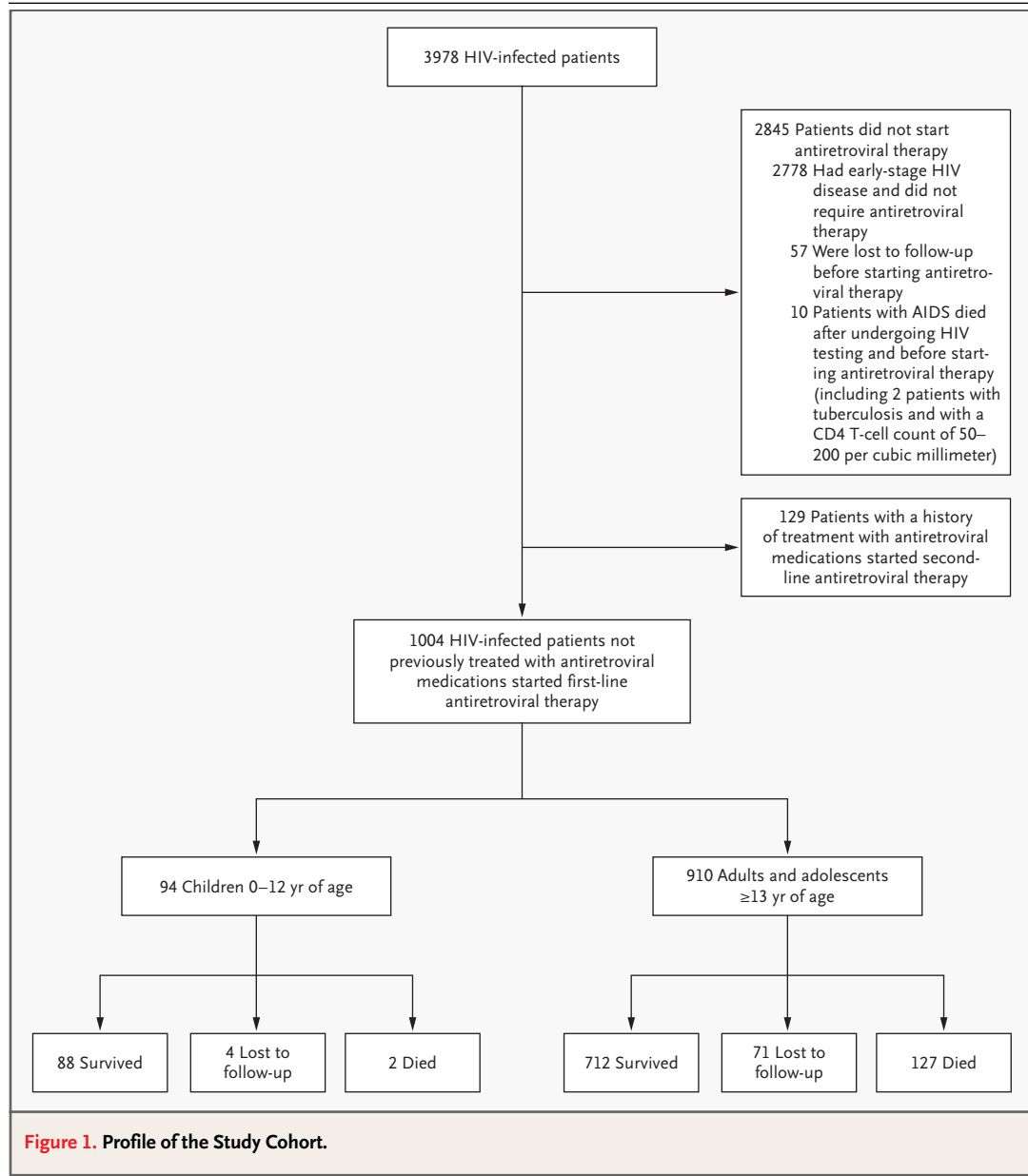
## RESULTS

#### ENROLLMENT

Between March 1, 2003, and April 30, 2004, GHESKIO provided HIV counseling, testing, and primary care to 23,394 patients, of whom 3978 (17 percent) were HIV-seropositive. Of these HIV-infected patients, 1004 (25 percent) who had not previously received treatment met the criteria for antiretroviral therapy, and therapy was initiated in these patients; 2778 (70 percent) had early-stage HIV disease and did not require antiretroviral therapy; 57 (1 percent) met the criteria for antiretroviral therapy but were lost to follow-up before therapy could be initiated; 129 (3 percent) had previously received antiretroviral therapy; and 10 (<1 percent) died after they were tested for HIV and before antiretroviral therapy could be initiated (Fig. 1). The mean enrollment rate was 80 new patients per month (range, 32 to 141). Enrollment continued after April 2004, and approximately 2500 patients are currently receiving antiretroviral therapy at GHESKIO. The baseline characteristics of the first 1004 patients and their initial antiretroviral-therapy regimens are provided in Table 1.

#### DISPOSITION OF PATIENTS AT THE TIME OF DATA ANALYSIS

At the time of data analysis, 800 of the 1004 patients (80 percent) were still being followed up, 75 (7 percent) had been lost to follow-up, and 129 (13 percent) had died. There was no difference in baseline characteristics (including age, sex, CD4 T-cell count, body weight, and stage of HIV infection) be-



tween patients who were lost to follow-up and those who were not. The most common reason for patients' becoming lost to follow-up was their leaving Port-au-Prince to return to their rural villages. The median follow-up time for the 1004 patients was 13 months. The cohort profile is shown in Figure 1.

**SURVIVAL**

Of the 910 adult and adolescent patients, 127 (14 percent) died. Of the 127 deaths, 55 (43 percent) were due to persistent wasting syndrome, 20 (16 percent) to tuberculosis, 6 (5 percent) to bacterial

pneumonia, 5 (4 percent) to toxoplasmosis, 4 (3 percent) to cancer, 4 (3 percent) to cryptosporidiosis, 4 (3 percent) to sepsis syndrome, 3 (2 percent) to congestive heart failure, 3 (2 percent) to trauma, and 23 (18 percent) to unknown causes. One hundred of the 127 deaths (79 percent) occurred within six months after the initiation of antiretroviral therapy. According to survival analysis, 90 percent of the patients were alive at 6 months and 87 percent at 12 months (Fig. 2). The factors present at the initiation of antiretroviral therapy that were predictors of death were the presence of an AIDS-defining ill-

**Table 1. Baseline Characteristics of Patients in Haiti Receiving Antiretroviral Therapy.**

Characteristic	Value	Characteristic	Value
<b>Adults and adolescents (N=910)</b>		<b>Children (N=94)</b>	
Female sex — no. (%)	504 (55)	Female sex — no. (%)	52 (55)
Age — no. (%)		Age — no. (%)	
13–19 yr	30 (3)	<1 yr	4 (4)
20–29 yr	120 (13)	1–4 yr	34 (36)
30–39 yr	352 (39)	5–12 yr	56 (60)
40–49 yr	290 (32)	Status of parents†	
>49 yr	118 (13)	Both dead	14 (15)
Resident of Port-au-Prince — no. (%)	816 (90)	1 Dead	41 (44)
Self-referred — no. (%)	419 (46)	Both alive	39 (41)
Income < \$1/day — no. (%)	513 (56)	AIDS-defining illness — no. (%)	44 (47)
Education — no. (%)		Tuberculosis — no. (%)	9 (10)
None	157 (17)	z Score for weight	
Primary school	281 (31)	Median	–1.8
Secondary school	404 (44)	Interquartile range	–2.6 to –1.1
College	68 (7)	CD4 T cells — %	
Marital status — no. (%)		Median	13
Common-law marriage	285 (31)	Interquartile range	8 to 20
Married	162 (18)	Hemoglobin — g/dl	
Separated	159 (17)	Median	9.5
Single	209 (23)	Interquartile range	8.8 to 10.2
Widowed	95 (10)	Initial antiretroviral-therapy regimen — no. (%)	
AIDS-defining illness — no. (%)*	472 (52)	Zidovudine, lamivudine, efavirenz	58 (62)
Tuberculosis — no. (%)	72 (8)	Zidovudine, lamivudine, nevirapine	22 (23)
Pregnant — no. (%)	22 (2)	Didanosine, lamivudine, efavirenz	8 (9)
Body weight — kg		Other	6 (6)
Men			
Median	55.7		
Interquartile range	48.9 to 62.0		
Women			
Median	48.9		
Interquartile range	43.0 to 55.7		
CD4 T-cell count — per mm <sup>3</sup>			
Median	131		
Interquartile range	55 to 211		
Hemoglobin — g/dl			
Median	10.6		
Interquartile range	9.2 to 11.6		
Initial antiretroviral-therapy regimen — no. (%)			
Zidovudine, lamivudine, efavirenz	428 (47)		
Zidovudine, lamivudine, nevirapine	381 (42)		
Zidovudine, lamivudine, abacavir	48 (5)		
Other	53 (6)		

\* AIDS-defining illnesses are those listed by the World Health Organization.<sup>19</sup>

† One third of surviving HIV-infected parents were also receiving antiretroviral therapy.

ness, a CD4 T-cell count under 50 per cubic millimeter, and a body weight in the lowest quartile for sex (Table 2).

Two of the 94 children died within one month after enrollment, one from a sepsis-like syndrome and the other from a respiratory tract infection of unknown cause. According to survival analysis, 98 percent of the cohort was alive at one year.

#### OTHER MEASURES OF TREATMENT RESPONSE

##### *Virologic Response*

Plasma HIV RNA was measured in adult and adolescent patients who had a 1-year follow-up visit (at 48 to 56 weeks) in December 2004. Plasma was available from 100 of the 117 adult and adolescent patients who had been followed for one year (85 percent). Viral load was less than 400 copies of HIV RNA per milliliter in 76 of the 100 patients tested. There were no significant differences in baseline characteristics between the 76 patients with fewer than 400 copies of HIV RNA per milliliter and the 24 patients with 400 or more copies per milliliter.

##### *CD4 T-Cell Response*

In adults and adolescents, the median increase in the CD4 T-cell count at six months was 128 per cubic millimeter (interquartile range, 62 to 197 per cubic millimeter). The CD4 T-cell count at six months was greater than the baseline value in 459 of 504 patients (91 percent) and remained the same or decreased from baseline in 45 (9 percent). The median increase in the CD4 T-cell count at 12 months

was 163 per cubic millimeter (interquartile range, 77 to 251 per cubic millimeter). The CD4 T-cell count at 12 months was greater than the baseline value in 360 of 397 patients (91 percent) and remained the same or decreased from baseline in 37 (9 percent). In children, the median CD4 T-cell percentage rose from a baseline value of 13 percent (interquartile range, 8 to 20 percent) to 21 percent (interquartile range, 16 to 29 percent) at 6 months and to 26 percent (interquartile range, 22 to 36 percent) at 12 months.

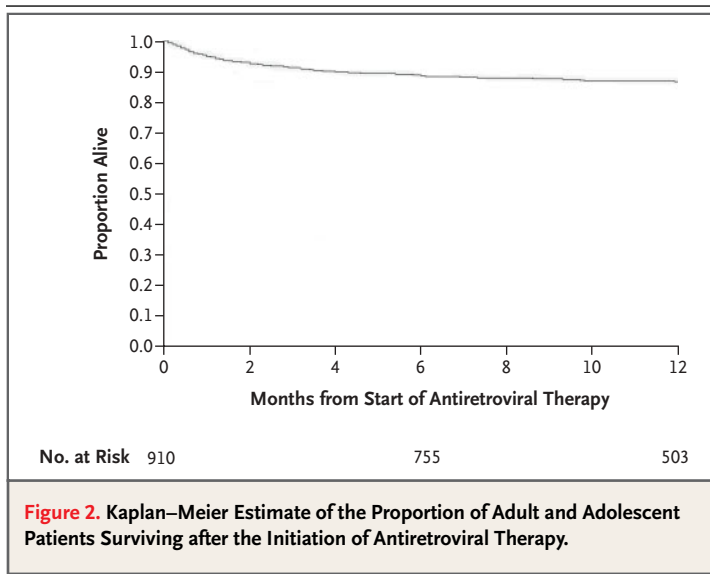
##### *Weight Gain*

At six months, adult and adolescent patients had gained a median of 4.0 kg (interquartile range, 0.9 to 7.7). At six months, 639 of 759 patients (84 percent) had gained weight, and 120 patients (16 percent) remained at the same weight or had lost weight. At 12 months, adult and adolescent patients had gained a median of 5.5 kg (interquartile range, 1.4 to 10.5). At 12 months, 396 of 466 patients (85 percent) had gained weight, and 70 (15 percent) remained at the same weight or had lost weight. In children, the z score for weight increased from a median value of  $-1.8$  (interquartile range,  $-2.6$  to  $-1.1$ ) at enrollment, to  $-1.3$  at 6 months (interquartile range,  $-1.9$  to  $-0.6$ ) and to  $-1.2$  at 12 months (interquartile range,  $-1.6$  to  $-0.4$ ).

#### TUBERCULOSIS

Of the 910 adult and adolescent patients, 113 (12 percent) received concurrent treatment for tuberculosis while receiving antiretroviral therapy, 72 (8 percent) began treatment for tuberculosis before beginning antiretroviral therapy, and 41 (5 percent) began treatment for tuberculosis after beginning antiretroviral therapy. Two patients with CD4 T-cell counts of 50 to 200 per cubic millimeter started tuberculosis treatment but died in the two-month period before they would have begun antiretroviral therapy (Fig. 1). Of the 113 patients who received concurrent treatment for tuberculosis while receiving antiretroviral therapy, 89 (79 percent) were cured of tuberculosis, 20 (18 percent) died, 1 (1 percent) did not respond to tuberculosis therapy, and 3 (3 percent) were lost to follow-up. There was no significant difference in survival between patients with and patients without tuberculosis.

Of the 72 patients who started tuberculosis treatment before antiretroviral therapy, 11 (15 percent) had a suspected immune reconstitution syn-



drome with temporary worsening of tuberculosis symptoms after beginning antiretroviral therapy, including recurrent fevers, increasing cough, and a draining lymph-node fistula; 4 were treated with corticosteroids. No patient stopped antiretroviral therapy because of the immune reconstitution syndrome.

Forty-one patients were found to have tuberculosis after beginning antiretroviral therapy; symptoms of tuberculosis commenced within three months after the initiation of antiretroviral therapy in 26 (63 percent). A weight loss of more than 5 percent at month 3 was associated with the diagnosis of tuberculosis after the initiation of antiretroviral therapy (odds ratio, 2.62; 95 percent confidence interval, 1.17 to 5.86;  $P=0.04$ ).

Among the 94 children, 13 (14 percent) received antiretroviral therapy with concurrent treatment for tuberculosis. Eleven of these 13 children (85 percent) appeared to have been cured of tuberculosis, and 2 (15 percent) were lost to follow-up; none of them died. There was no significant difference in survival between children with and without tuberculosis.

#### FIRST-LINE MEDICATION CHANGES AND TOXIC EFFECTS

Of the 910 adult and adolescent patients, 229 (25 percent) required a change in a first-line medication. The reasons for the change were toxic effects in 102 patients (11 percent), disruption in the medication supply in 66 patients (7 percent), sexual activity by women of reproductive age in 29 patients (3 percent), suspected treatment failure in 11 patients (1 percent), and tuberculosis in 21 patients (2 percent). The disruptions in medication supply occurred when international suppliers were months late in delivering medications.

Table 3 shows the treatment-limiting toxic effects of first-line medications. Anemia and central nervous system symptoms were the most common. Two patients had the Stevens–Johnson syndrome, one of whom died; nevirapine was the suspected cause in both cases. Gynecomastia, in several cases accompanied by lactorrhea, occurred in 15 men receiving efavirenz. According to Kaplan–Meier survival analysis, 14 percent of the adult and adolescent patients required a change in first-line medication because of a toxic effect during the first 12 months of antiretroviral therapy.

Of the 94 children, 9 (10 percent) required a medication change: 5 because of toxic effects, 1 be-

**Table 2. Predictors of Death among Adults and Adolescents Who Were Receiving Antiretroviral Therapy.**

Predictor	Hazard Ratio (95% CI)*	P Value
AIDS-defining illness†	2.1 (1.7–2.5)	<0.001
CD4 T-cell count <50/mm <sup>3</sup>	1.6 (1.1–2.1)	0.04
Body weight in lowest quartile for sex‡	3.3 (2.9–3.7)	<0.001

\* Hazard ratios have been adjusted for age and for the other variables listed in the table. CI denotes confidence interval.

† AIDS-defining illnesses are those listed by the WHO.<sup>19</sup>

‡ The lowest quartile for body weight is <48.9 kg for men and <43 kg for women.

cause of a disruption in medication supply, and 3 because of tuberculosis treatment. Of the five children whose medication was changed because of a toxic effect, two receiving zidovudine had anemia, one receiving nevirapine had a rash, one receiving efavirenz had hepatitis, and one receiving efavirenz had gynecomastia.

#### DISCUSSION

Antiretroviral therapy was initiated in 1004 patients with AIDS within 14 months after international funds for therapy became available in Haiti. This large cohort was consecutively enrolled, had high rates of poverty, malnutrition, and tuberculosis, and was similar to clinic populations that would be found in other urban areas severely affected by HIV disease in the Caribbean or sub-Saharan Africa. The one-year survival was 87 percent for adults and adolescents and 98 percent for children. In comparison, the one-year survival without antiretroviral therapy for adults and children with AIDS in Haiti and other developing countries is about 30 percent.<sup>22–24</sup> This rapid and effective large-scale introduction of antiretroviral therapy in the poorest country in the Western Hemisphere, even during times of political unrest, provides evidence in support of international efforts to make antiretroviral therapy available to patients with AIDS worldwide.

The virologic response rate of 76 percent (with a response defined as <400 copies of HIV RNA per milliliter) and the median increase in the CD4 T-cell count of 163 per cubic millimeter at one year in adults and adolescents are similar to results from the United States. In a meta-analysis of clinical trials involving adults not previously treated with antiretroviral therapy who received a three-drug antiretroviral-therapy regimen that included a nonnucleoside reverse-transcriptase inhibitor,

**Table 3. Treatment-Limiting Toxic Effects of First-Line Antiretroviral Medications in 910 Adults and Adolescents in Haiti.**

Medication	Patients Initiating Treatment	Toxic Effect	Patients Stopping Treatment
	no.		no. (%)
Zidovudine	866	Anemia	41 (5)
Efavirenz	452	Central nervous system symptoms	25 (6)
		Gynecomastia	15 (3)
		Rash	3 (<1)
		Nausea	2 (<1)
		Hepatitis*	1 (<1)
Nevirapine	401	Rash†	11 (3)
		Nausea	2 (<1)
		Hepatitis*	1 (<1)
Abacavir	55	Rash	1 (2)

\* Both cases of hepatitis occurred in patients who were receiving concurrent treatment for tuberculosis.

† Two patients with the Stevens–Johnson syndrome are included.

the virologic response rate (<400 copies of HIV RNA per milliliter) at 48 weeks was 72 percent and the mean increase in the CD4 T-cell count was 174 per cubic millimeter.<sup>25,26</sup> An analysis of the 12-month outcomes of patients beginning antiretroviral therapy in 2001 and 2002 in a Baltimore clinic found a virologic response rate (<400 copies of HIV RNA per milliliter) of 68 percent and a mean increase in the CD4 T-cell count of 139 per cubic millimeter.<sup>27,28</sup>

The rates of treatment-limiting toxic effects in our patients were similar to those reported for patients from developed countries who were treated with similar regimens.<sup>29,30</sup> Despite recent concern about nevirapine toxicity,<sup>31</sup> less than 1 percent of the patients in our cohort who were treated with nevirapine had hepatitis. Nevirapine-induced hepatitis has been associated with a CD4 T-cell count of more than 250 per cubic millimeter, but the count in most of our patients was less than 200 per cubic millimeter. Among the patients who began therapy with efavirenz, treatment-limiting toxic effects occurred in 10 percent, a rate higher than that reported from the United States. Most Haitians are of African descent, and a recent study demonstrated that people of African descent are at greater risk than others for central nervous system side effects from efavirenz.<sup>32</sup> An additional 6 percent of pa-

tients who began therapy with efavirenz stopped because of the risk of teratogenicity in sexually active women. Alternatives to first-line regimens containing efavirenz may be especially important for populations of African origin with large numbers of sexually active women.

The challenges involved in providing antiretroviral therapy in developing countries include high rates of poverty, malnutrition, and tuberculosis. The majority of our patients earned less than \$1 a day, the World Bank's international poverty line.<sup>33</sup> Poverty affects all aspects of care, including patients' ability to buy food, obtain access to clean water and housing, and pay for transportation to the clinic. We have therefore striven to integrate our antiretroviral-therapy program with existing social programs. There is a growing body of evidence that malnutrition is a critical cofactor in AIDS progression in resource-poor countries.<sup>34,35</sup> In our cohort, low baseline body weight was an independent predictor of death. We therefore provided a daily multivitamin supplement to all of our patients who were receiving antiretroviral therapy and a monthly stock of rice, beans, and vegetable oil to the most undernourished patients. Twelve percent of our patients who were receiving antiretroviral therapy received concurrent treatment for tuberculosis. Data from this study suggest that a failure to gain weight after three months of antiretroviral therapy should prompt an evaluation for tuberculosis. Patients with tuberculosis had a survival rate similar to that of patients without tuberculosis.

The single greatest logistic challenge was maintaining the supply of antiretroviral drugs. Delays in delivery resulted in a change in the antiretroviral-therapy regimen for 7 percent of our patients. Developing reliable manufacturing and distribution systems for antiretroviral drugs is an urgent international priority. Other logistic challenges may arise in different developing countries.

We estimated the overall cost of treating a patient with antiretroviral therapy to be about \$1,600 per year, with antiretroviral medications accounting for 35 to 45 percent of the total. The care of the 1004 patients receiving antiretroviral therapy was supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). However, there are a number of other, intangible factors that significantly contributed to the successful implementation of this program, including continuity of

leadership, international collaboration, and dedication of GHESKIO personnel who provided care to poor patients with AIDS in an urban slum, even during times of violent political unrest. These factors are the product of infrastructure development, personnel training, and mentorship, which are critical for scaling up antiretroviral therapy. The treatment outcomes achieved in Haiti were similar to those achieved in U.S. clinics, providing evidence in support of international efforts to make antiretroviral therapy available in developing countries. Finally, the sustainability of programs in Haiti and

in other impoverished countries is absolutely dependent on continued international support.

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## REFERENCES

- Scaling up antiretroviral therapy in resource-limited settings. Geneva: World Health Organization, 2004.
- Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. April 7, 2005. Washington, D.C.: Government Printing Office, 2005. (Accessed November 3, 2005, at [http://aidsinfo.nih.gov/guidelines/adult/AA\\_040705.pdf](http://aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf).)
- Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus didanosine in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* 1997;337:725-33.
- Mouton Y, Alfandari S, Valette M, et al. Impact of protease inhibitors on AIDS-defining events and hospitalizations in 10 French AIDS reference centers. *AIDS* 1997;11:F101-F105.
- Gulick RM, Mellors JW, Havlir D, et al. Treatment with didanosine, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* 1997;337:734-9.
- Cameron DW, Heath-Chiozzi M, Daner S, et al. Randomised placebo-controlled trial of zalcitabine in advanced HIV-1 disease. *Lancet* 1998;351:543-9.
- Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;338:853-60.
- Farmer P, Leandre F, Mukherjee JS, et al. Community-based approaches to HIV treatment in resource-poor settings. *Lancet* 2001;358:404-9.
- Weidle PJ, Malamba S, Mwebaze R, et al. Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. *Lancet* 2002;360:34-40.
- Adje-Toure C, Celestin B, Hanson D, et al. Prevalence of genotypic and phenotypic HIV-1 drug-resistant strains among patients who have rebound in viral load while receiving antiretroviral therapy in the UNAIDS-Drug Access Initiative in Abidjan, Cote d'Ivoire. *AIDS* 2003;17:Suppl 3:S23-S29.
- Coetzee D, Hildebrand K, Boule A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004;18:887-95.
- Hofer CB, Schecter M, Harrison LH. Effectiveness of antiretroviral therapy among patients who attend public HIV clinics in Rio de Janeiro, Brazil. *J Acquir Immune Defic Syndr* 2004;36:967-71.
- Institute of Medicine. Scaling up treatment for the global AIDS pandemic. Washington, D.C.: National Academies Press, 2005:75-9.
- World Bank. Haiti at a glance. (Accessed November 3, 2005, at [http://www.worldbank.org/data/countrydata/aag/hti\\_aag.pdf](http://www.worldbank.org/data/countrydata/aag/hti_aag.pdf).)
- Pape JW, Liautaud B, Thomas F, et al. Characteristics of the acquired immunodeficiency syndrome (AIDS) in Haiti. *N Engl J Med* 1983;309:945-50.
- Pape J, Johnson WD Jr. AIDS in Haiti: 1982-1992. *Clin Infect Dis* 1993;17:Suppl 2:S341-S345.
- Institut Haitien de l'Enfance, Centres GHESKIO. Etude de sero-surveillance par methode sentinelle de la prevalence du VIH, de la syphilis, et de l'hepatite B chez les femmes enceintes en Haiti 1999-2000. Port au Prince, Haiti: Pan American Health Organization, 2001.
- Peck R, Fitzgerald DW, Liautaud B, et al. The feasibility, demand, and effect of integrating primary care services with HIV voluntary counseling and testing: evaluation of a 15-year experience in Haiti, 1985-2000. *J Acquir Immune Defic Syndr* 2003;33:470-5.
- WHO case definitions for AIDS surveillance in adults and adolescents. *Wkly Epidemiol Rec* 1994;37:273-5.
- Treatment of tuberculosis. *MMWR Recomm Rep* 2003;52(RR-11):1-77. [Erratum, *MMWR Morb Mortal Wkly Rep* 2005;53:1203.]
- Koenig SP, Leandre F, Farmer PE. Scaling-up HIV treatment programmes in resource-limited settings: the rural Haiti experience. *AIDS* 2004;18:Suppl 3:S21-S25.
- Deschamps MM, Fitzgerald DW, Pape JW, Johnson WD Jr. HIV infection in Haiti: natural history and disease progression. *AIDS* 2000;14:2515-21.
- Jean SS, Pape JW, Verdier RI, et al. The natural history of human immunodeficiency virus 1 infection in Haitian infants. *Pediatr Infect Dis J* 1999;18:58-63.
- Schneider M, Zwahlen M, Egger M. Natural history and mortality in HIV positive individuals living in resource poor settings: a literature review: UNAIDS Obligation HQ/03/463871. (Accessed November 3, 2005, at <http://www.epidem.org/publications.htm>.)
- Bartlett JA, DeMasi R, Quinn J, Moxham C, Rousseau F. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS* 2001;15:1369-77.
- Bartlett J, Fath M, DeMasi R, Quinn J, Hermes A, Rousseau F. An updated meta-analysis of triple combination therapy in antiretroviral-naive HIV-1 infected adults. Presented at the 12th Conference on Retroviruses and Opportunistic Infections, Boston, February 22-25, 2005. abstract.
- Lucas GM, Chaisson RE, Moore RD. Survival in an urban HIV-1 clinic in the era of highly active antiretroviral therapy: a 5-year cohort study. *J Acquir Immune Defic Syndr* 2003;33:321-8.
- Moore RD, Keruly JC, Gebo KA, Lucas GM. An improvement in virologic response to highly active antiretroviral therapy in clinical practice from 1996 through 2002. *J Acquir Immune Defic Syndr* 2005;39:195-8.
- Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA* 2004;292:191-201.
- Gulick RM, Ribaud HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004;350:1850-61.
- Clarification of risk factors for severe, life-threatening and fatal hepatotoxicity with VIRAMUNE (nevirapine). Ridgefield, Conn.:

Boehringer Ingelheim, February 2004 (letter to health care professionals).

32. Haas DW, Ribaud HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004;18:2391-400.

33. World Bank. Beyond economic growth: glossary. (Accessed November 3, 2005, at <http://www.worldbank.org/depweb/english/beyond/global/glossary.html#52>.)

34. 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.

35. Fawzi W, Msamanga G, Spiegelman D, Hunter DJ. Studies of vitamins and minerals and HIV transmission and disease progression. *J Nutr* 2005;135:938-44.

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