Evaluating Adherence to Highly Active Antiretroviral Therapy with Use of Pill Counts and Viral Load Measurement in the Drug Resources Enhancement against AIDS and Malnutrition Program in Mozambique

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Background. Maintaining treatment adherence among the growing number of patients receiving antiretroviral treatment in Africa is a dramatic challenge. The objective of our study was to explore the results of a computerized pill count method and to test the validity, sensitivity, and specificity of this method with respect to viral load measurement in an African setting.

Methods. We performed a prospective, observational study involving patients who received first-line highly active antiretroviral therapy in Mozambique from 1 April 2005 through 31 March 2006. Enrolled patients had received treatment for at least 3 months before the study. For defining treatment adherence levels, pill counts were used, and the results were analyzed with viral load measurements at the end of the observation period.

Results. The study involved 531 participants. During the 12 months of observation, 137 patients left the program or discontinued first-line therapy. Of the remaining 394 patients, 284 (72.1%) had >95% treatment adherence; of those 284 patients, 274 (96.5%) had a final viral load <1000 copies/mL. A Cox proportional hazards analysis revealed that the relationship between >95% treatment adherence and the final viral load was closer than that between >90% treatment adherence and viral load.

Conclusions. Treatment adherence >95% maximizes the results of the nonnucleoside reverse-transcriptase inhibitor–based regimen. The pill count method appears to be a reliable and economic tool for monitoring treatment adherence in resource-limited settings.

From the end of 2002 through June 2006, the number of persons receiving antiretroviral therapy (ART) in sub-Saharan Africa increased from ~50,000 to >1 million [1]. Preventative measures must be taken now to offset the eventuality of large numbers of patients experiencing first-line treatment failure [2]. Optimal treatment adherence is crucial for viral suppression [3–5] to prevent the evolution from HIV infection to AIDS [6] and progression to death [7–8].

In general, in Africa, first-line ART consists of 2 nucleoside analog reverse-transcriptase inhibitors and 1 nonnucleoside reverse-transcriptase inhibitor (NNRTI), with the aim of making treatment receipt simple to improve adherence rates. Among patients who have moderate-to-high levels of treatment adherence, NNRTI resistance has been less common than protease inhibitor resistance, because rates of viral suppression have been significantly higher in the NNRTI-treated group [9–14].

Determining the threshold of HAART adherence is

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crucial for maintaining viral suppression replication over time [9, 15, 16]. No gold standard has been established for monitoring HAART adherence, and the various current methods for measuring treatment adherence lack homogeneity. Self-reports and interviews are helpful for identifying some of the reasons for a patient's noncompliance with the treatment regimen [17–20] but are inadequate when used alone, because they tend to overestimate treatment adherence. Pill counts and the Medication Event Monitoring System are considered to be more useful [21–26], but validation research comparing the results of pill count methods and the Medication Event Monitoring System on the basis of an objective parameter, such as viral load, is lacking in the scientific literature, particularly in the context of the African setting [27].

The aim of our study was to contribute to research about HAART adherence in Africa by looking specifically at patients receiving the first-line treatment regimen and at pill counts monitored frequently over time using specially designed computer software. The objective was to test the validity, sensitivity, and specificity of the pill count method with respect to viral load measurement and to explore other factors threatening high treatment adherence levels.

METHODS

The Drug Resource Enhancement against AIDS and Malnutrition (DREAM) Program. The study was performed in the context of the DREAM Program, which was launched and managed by the Community of Sant'Egidio in Mozambique in 2002. Thirteen DREAM centers now operate in Mozambican national health structures and in 9 other African countries [28–32].

The participation of HIV-infected patients is strengthened with free treatment and testing, nutritional support, and home care. Feedback comes from (1) measurement of viral load every 6 months and CD4 cell count every 3 months and biochemistry testing to monitor for adverse reactions every 3 months; (2) clinical examinations and frequent follow-up visits to assess general health indicators, such as body mass index (calculated as the weight in kilograms divided by the square of the height in meters) and hemoglobin level; and (3) home visits, counseling, and meetings involving the entire treatment and support team.

Community health care workers help to increase treatment adherence by seeking out patients who do not have optimal levels of adherence. This is done most efficiently through home visits, which allow for a more complete assessment of the patient's needs. The home visits and other adherence interventions are simple, replicable, and cost only ~US$10 per year for each patient.

Although the program requires a significant initial investment (~US$400,000) for the molecular biology laboratory, the costs for tests and antiretroviral drugs are fairly low. First-line treatment costs US$350 per year for each patient, and second-line treatment costs US$900 per year. The total cost includes laboratory costs of ~US$75 per year for each patient. The current annual cost for generic antiretroviral drugs is ~US$160 for each patient who receives first-line treatment and ~US$720 for each patient who receives second-line treatment.

Study population. Study participants were patients being treated at the Machava DREAM center in a National Health Service day hospital in Matola, Mozambique, a southern dormitory town with ~700,000 residents. The catchment area covers a radius of ~30 km around the treatment center.

Study design. This was a prospective, single-arm, observational study. The period of observation was 12 months. The enrollment period lasted 20 days (10–30 March 2005). The study was conducted among patients served by the DREAM Program at a public hospital.

Participant selection. Included in the study were all of the patients at the Machava DREAM treatment center who were aged >15 years as of 1 April 2005 and who were receiving first-line ART. The treatment involved a fixed-combination drug regimen, including 2 nucleoside analog reverse-transcriptase inhibitors (lamivudine and zidovudine or stavudine) and 1 NNRTI (nevirapine), given as 2 pills per day for a period ⩾3

Table 1. Treatment adherence among 137 patients observed for <12 months from the beginning of the observation period.

Patient status	No. of patients	Duration of HAART exposure before the beginning of the observation period, mean months	Percentage of patients who had >95% treatment adherence	Treatment adherence, mean % ± SD
Quit the program	17	9.6	47.1	85.4 ± 19.8
Switched from a first-line therapy regimen	71	15.4	66.2	94.6 ± 7.8
Because of toxicity events	44	9.6	61.7	94.0 ± 6.8
Because of virological failure	27	24.8	73.5	95.6 ± 10.2
Died	8	11.9	37.5	93.4 ± 7.9
Moved to another AIDS center	41	14.4	65.9	91.9 ± 14.2

Table 2. Characteristics of 394 patients observed for 12 months.

Percentile	Age at the beginning of the observation period, years	Duration of HAART exposure before the beginning of the observation period, months	CD4 cell count, cells/μL		Viral load, copies/mL	
			At the beginning of the observation period	At the end of the observation period	At the beginning of the observation period	At the end of the observation period
25th	31	6	243	281	<50	<50
50th	37	10	338	387	<50	<50
75th	43	22	451	520	4450	<50

NOTE. One hundred sixty-one patients were male, and 233 patients were female.

months. Patients who had received <3 months of therapy before the start of the observation period were excluded, because the aim of the study was to evaluate long-term treatment adherence.

Outcome measurement. The primary end point chosen for this analysis was viral load ⩾1000 copies/mL after the end of the observation period (12 months). Viral load was measured using branched DNA technology (System 340, version 3.0; Bayer Diagnostic). For this study, we used the most recent viral load measured (within 90 days) before the date of the start of observation and the first available viral load (within 60 days) after the end of the observation period.

Treatment adherence measurement using computerized pill counts. The measurement of treatment adherence was based on pill counts recorded on computer software every 30 days. The software showed each patient's HAART regimen, according to the active ingredient or combination, and calculated treatment adherence as the percentage of the number of pills prescribed and consigned for the period between appointments, compared with the number of pills returned at the following appointment. The calculation, based on an individual's prescription for pills needed for full coverage, also took into account days of missed coverage if the patient did not arrive on the assigned day to receive a new supply of medication.

The pharmacist met each patient each month and inquired about how the drugs were taken (with particular attention to time tables and meal times) and about adverse reactions or other problems. The pills that were not taken were returned, and the data were entered into the software. The supply for the next 30 days was then given to the patient. The software indicated to the pharmacist exactly how many pills the patient would need before his or her next appointment, and it did not allow the pharmacist to continue to the next patient until all of the data relating to the treatment adherence of the current patient was entered.

Statistical analysis. To assess the risk associated with ⩽95% treatment adherence, stratified by the duration of HAART exposure, the Mantel-Haenszel procedure was used to estimate the pooled OR for all strata. The adopted formula is as follows:

$$OR_{MH} = \frac{\sum_{i-1}^{k}\left(\frac{a_i d_i}{n_i}\right)}{\sum_{i-1}^{k}\left(\frac{b_i c_i}{n_i}\right)}$$

To calculate the specificity and sensitivity of 95% treatment adherence, receiver operating characteristic curves were designed. A Cox proportional hazard model was used to calculate the hazard ratios of having a viral load ⩾1000 copies/mL in relation to differing initial CD4 cell count, age, and treatment adherence level. The validity of proportionality assumption for the model was verified. Statistical analysis was conducted using SPSS, version 14 (SPSS).

RESULTS

Based on the criteria mentioned above, 531 patients were selected for the study, including 222 male and 309 female patients. The mean age (±SD) was 36.2 ± 9.0 years. For the male patients, the mean age (±SD) was 37.9 ± 9.5 years, and for the female patients, the mean age (±SD) was 35.0 ± 8.5 years. The mean and median durations of HAART before the beginning of the observation period were 14.7 months and 8 months, respectively. Of the 531 patients selected for the study, 137 either left the program or discontinued first-line treatment before the

Table 3. Treatment adherence among 394 patients observed for 12 months.

Patient group, by treatment adherence	No. (%) of patients (n = 394)
>95%	284 (72.1)
91%–95%	66 (16.7)
86%–90%	22 (5.6)
81%–85%	11 (2.8)
76%–80%	4 (1.0)
<76%	7 (1.8)
All	394 (100.0)

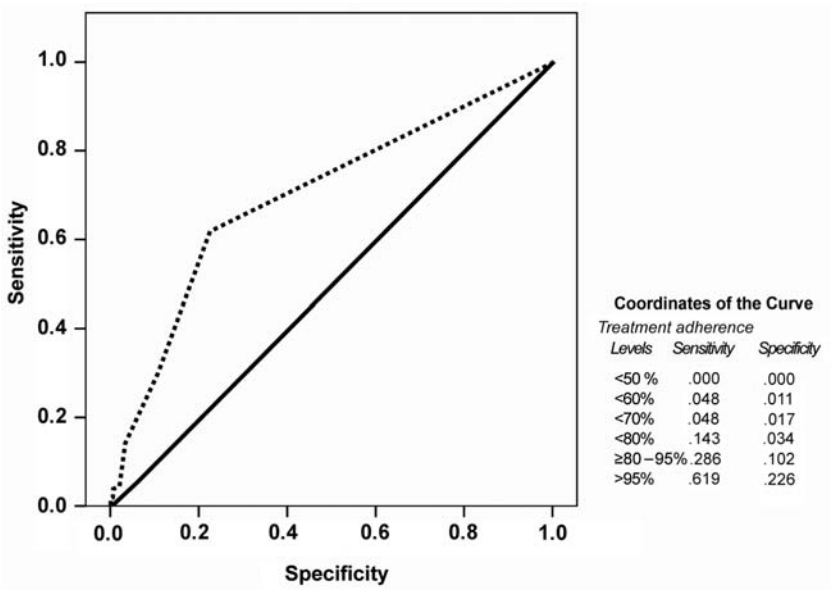

Figure 1. Receiver operating characteristic curve showing the relationship between treatment adherence and viral load <1000 copies/mL for the 236 patients who had 15–27 months of HAART exposure at the end of the observation period.

end of the observation period, and the other 394 patients completed the 12-month period while receiving first-line therapy.

Of the 137 patients who were observed for <12 months (table 1), 8 (1.5%) died, 17 (3.2%) quit the program, 41 (7.7%) moved to health care centers in other areas of the country, and 71 (13.4%) shifted from the first-line regimen because of toxicity events (44 patients, including 21 because of anemia, 8 because of rash, and 15 because of grade 2–4 hepatic alterations) or virological failure (27 patients). For the patients who left the program before the end of the observation period, pill counts were calculated for the time that they participated. The mean period of observation ($\pm$SD) for the group was 5.8 $\pm$ 2.1 months. Because these patients did not remain in the study, it was not possible to compare their pill counts with the viral load measurement foreseen at the end of the 12-month observation period.

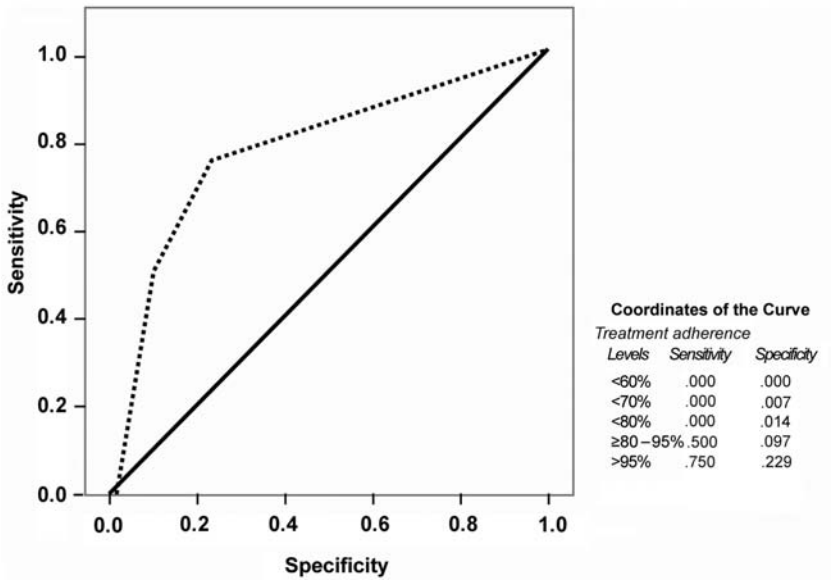

Figure 2. Receiver operating characteristic curve showing the relationship between treatment adherence and viral load <1000 copies/mL for 158 patients who had >27 months of HAART exposure at the end of the observation period.

Table 4. Treatment adherence, by duration of HAART exposure and viral load at the end of the observation period, for 394 patients observed for 12 months.

Duration of HAART exposure, viral load	Proportion of patients (%)		
	Who had ≤95% treatment adherence	Who had >95% treatment adherence	All
15–27 months			
≥1000 copies/mL	14/71 (19.7)	9/165 (5.5)	23/236 (9.7)
<1000 copies/mL	57/71 (80.3)	156/165 (94.5)	213/236 (90.3)
All	71/71 (100)	165/165 (100)	236/236 (100)
>27 months			
≥1000 copies/mL	4/39 (10.3)	1/119 (0.8)	5/158 (3.2)
<1000 copies/mL	35/39 (89.7)	118/119 (99.2)	153/158 (96.8)
All	39/39 (100)	119/119 (100)	158/158 (100)

To compare the pill counts with viral load at the end of the observation period, only those patients who were still receiving first-line treatment at the end of the observation period were taken into account. This group was composed of 394 patients, including 161 male and 233 female patients (table 2). At the beginning of the observation period, the mean age in this group was 37.0 years, and the mean duration of exposure to HAART was 14.1 months. Of the 394 patients, 284 (72.1%) had treatment adherence >95%; 66 (16.7%) had treatment adherence of 91%–95%; 22 (5%) had treatment adherence of 86%–90%; and 22 (5%) had treatment adherence <80% (table 3). The mean treatment adherence (± SD) was 95.2% ± 6.9%.

With regard to the final viral load measurements in relation to treatment adherence >95% and ≤95%, of the 284 patients who had treatment adherence >95%, 274 (96.5%) had a viral load <1000 copies/mL at the end of the observation period; of the 110 patients who had treatment adherence ≤95%, 92 (83.6%) had a viral load <1000 copies/mL at the end of the observation period.

The 236 patients who had received HAART for 15–27 months at the end of the observation period and the 158 patients who had received HAART for >27 months at the end of the observation period were also examined separately (table 4). In the group of patients who had >27 months of HAART exposure and treatment adherence ≤95%, the risk of having a viral load >1000 copies/mL at the end of the observation period was 13.5 (95% CI, 1.46–124.61), compared with 4.26 (95% CI, 1.75–10.37) in the group of patients who had 15–27 months of HAART exposure and treatment adherence ≤95%. Considering the group as a whole and adjusting for the duration of HAART exposure (using the Mantel-Haenszel test to determine estimated ORs and 95% CIs), the risk of patients who had treatment adherence ≤95% having a viral load ≥1000 copies/mL at the end of the observation period, compared with patients who had treatment adherence >95%, was 5.11 (95% CI, 2.26–11.54).

Subsequently, a comparison of sensitivities and specificities was performed for levels of adherence, classified by pill counts. The duration of exposure to HAART was taken into account in this analysis, as well.

The sensitivity and specificity of treatment adherence >95% were 61.9% and 77.4%, respectively, in the group of patients who had 15–27 months of HAART exposure. In the group of patients who had >27 months of HAART exposure, the sensitivity and specificity of >95% treatment adherence were 75% and 77.1%, respectively. The same processing for an 80%–95% treatment adherence yielded a sensitivity of 28.6% and a specificity of 89.8% for the group that received 15–27 months of HAART and a sensitivity of 50% and a specificity of 90.3% for the group that received >27 months of HAART.

The 2 receiver operating characteristic curves (figures 1 and 2) show that the relationship between >95% treatment adherence and a final viral load <1000 copies/mL is closer than that between >90% treatment adherence and a viral load <1000 copies/mL in both the group that received 15–27 months of HAART and the group that received >27 months of HAART.

Because viral load and treatment adherence appear to be correlated (although the correlation shows some variability), we sought to identify other possible factors associated with the risk of having a viral load ≥1000 copies/mL over time. Cox proportional hazards regression was performed with a viral load ≥1000 copies/mL as the outcome. The model was realized using the forward stepwise method. As shown in table 5, the variables

Table 5. Cox proportional hazards regression for viral load ≥1000 copies/mL in 394 patients observed for 12 months.

Variable	Hazard ratio (95% CI)	*P*
Age <30 years	2.185 (1.019–4.684)	<.045
CD4 cell count <338 cells/mm^3 at the beginning of the observation period	2.985 (1.260–7.072)	<.013
Treatment adherence >95%	4.518 (2.081–9.813)	

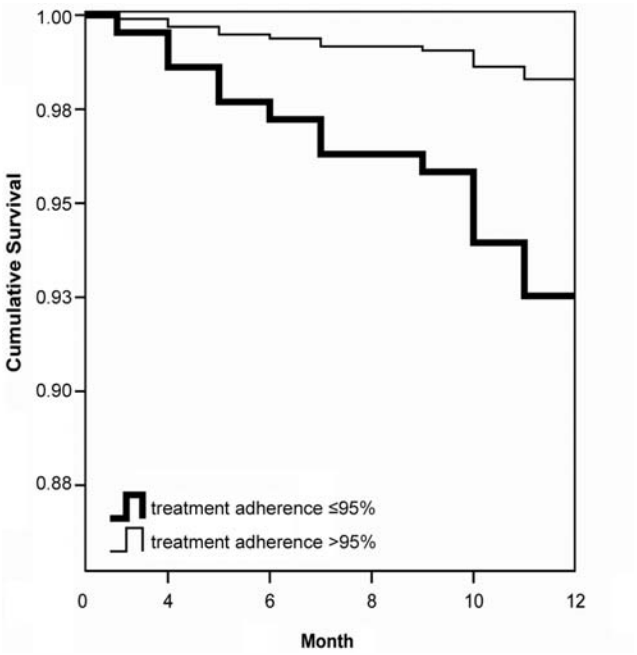

Figure 3. Cox proportional hazards regression showing cumulative survival over time among the 394 patients who received a first-line HAART regimen and were observed for 12 months.

identified as most significant by the model were treatment adherence >95%, (hazard ratio, 4.52; 95% CI, 2.08–9.81), age <30 years (hazard ratio, 2.18; 95% CI, 1.02–4.68), and CD4 cell count at the start of the observation period (hazard ratio, 2.98; 95% CI, 1.26–7.07). The model found 2 variables other than treatment adherence that were significantly associated with having a viral load ⩾1000 copies/mL: age <30 years and initial CD4 cell count <338 cells/mm^3 (the mean CD4 cell count in the cohort) (table 5 and figure 3).

DISCUSSION

The approach of the DREAM Program, briefly described above, provided good results, as demonstrated by viral load measurements, mortality, and dropout rates. It should be stressed that these results are relative to a mean duration of HAART of >2 years and that they were obtained in a context of nonexperimental, routine treatment activities in a health care center of the Mozambican National Health Service. Mozambique's national strategic plan for combating AIDS has progressively approached the diagnostic and therapeutic protocols of European countries, the same standards that the DREAM Program adopted from the beginning, with the help of private resources. To date, the Ministry of Health is particularly committed to ensuring that the protocols used in large cities and towns also become the standard in the more rural parts of the country. Guaranteeing equal standards, however, will require a serious improvement in infrastructure, including communications, transportation, and the distribution of efficient, properly equipped laboratories throughout the country. Since 2004, the Ministry of Health's AIDS program and its affiliated DREAM Program have been receiving economic support from the World Bank, President's Emergency Plan for AIDS Relief, and several government overseas development funds, particularly those from France.

A crucial element of the DREAM Program is the attention paid to treatment adherence by patients and the factors that influence and modify treatment adherence over time. All persons involved in the treatment process, particularly the patients, must have correct and updated information about treatment adherence levels, and the information must be available to those who prescribe and monitor treatment.

As a measurement of treatment adherence, the results of the pill count method were clearly in agreement with the data supplied by viral load measurements, and such a method can be recommended as a reliable tool that is both replicable and economical. The results far exceed those obtained with self-reports or an administered questionnaire and are at least comparable with those supplied by the Medication Event Monitoring System, which is difficult to use in resource-limited settings. Pill counts become even more useful for health care workers when the counts are combined with other information about the patient's treatment adherence.

The possibility of maintaining an undetectable viral load or the risk of deterioration was present for all of the patients, even when stratified by the duration of HAART use (table 4), but the relationship between treatment adherence and viral load was especially clear in patients receiving therapy for >2 years. This may be attributable to the 2 following considerations: a sort of natural selection of the patients who are most adherent to treatment becomes evident over time or prolonged exposure to HAART possibly reduces the levels of drug tolerance that may be observed in patients at the start of treatment.

The study may be seen as limited, because it includes the observation only of patients who received first-line HAART. The patients who switched to second-line HAART were observed for a shorter period, and the complete pill counts and viral load measurements were not available for many of them. A separate study will be dedicated to this group of patients. A second limitation is connected to the fact that pill counts do not record whether the patient actually consumed the pills; the patients could have sold the pills, shared them with others, or destroyed them, rather than returning them to the clinic. However, this limitation is partially mitigated by other methods of verifying whether the patient's level of treatment adherence was as high as reported; such methods included monitoring the percentage of medical appointments made and attended, the

level of participation in the center's educational activities, and the patients' response to periodic interviews regarding treatment adherence. In addition, variables for the general health condition of the patient, particularly body mass index and hemoglobin levels, were routinely determined and provided further indications about treatment adherence.

In the face of the increase in the observable risk for patients who have suboptimal treatment adherence, the analysis of the receiver operating characteristic curves shows a residual consistent variability. The pill counts reported in the research were determined monthly throughout the entire duration of the observation period and, thus, represent a punctual measurement of the number of days of lost therapy. This excludes the presence of a measurement bias of the pill counts and strengthens the convictions that other variables contribute to the formation of good treatment adherence.

The results of the Cox analysis, which demonstrated the statistical significance of 2 variables (initial CD4 cell count and age <30 years) on having a viral load ⩾1000 copies/mL as an outcome at the end of the observation period, require explanation. These 2 factors may be interpreted as follows: CD4 cell count may be a marker of the progression of disease and health status, and age <30 years may be a behavioral marker relating to a population that is young but widely represented in the context of the epidemic.

Treatment adherence >95% should be encouraged to maximize the results of the NNRTI-based regimen. Recording pill counts appears to be a reliable, economic, and timely tool for monitoring treatment adherence in resource-limited settings, especially when combined with other indirect treatment adherence indicators (such as appointments attended, body mass index, and hemoglobin level). Measuring viral load represents the preferred method for evaluating treatment adherence, and viral load is the main indicator of the risk of therapeutic failure, with evident advantages for making decisions regarding the appropriate treatment for patients. In addition, looking toward the future, there are economic advantages linked to avoiding second-line therapy and containing the impact of drug resistance on the health of patients and the entire population.

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