Antiretroviral Durability and Tolerability in HIV-Infected Adults Living in Urban Kenya

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Background: Insufficient data exist on the durability and tolerability of first-line antiretroviral therapy (ART) regimens provided by HIV treatment programs implemented in developing countries.

Methods: Longitudinal observation of clinical, immunologic, and treatment parameters of all HIV-infected adult patients initiated on ART was performed at Saint Mary's Mission Hospital in Nairobi, Kenya from September 2004 until August 2006.

Results: A total of 1286 patients were analyzed (59.1% female). Initial ART regimens were primarily stavudine, lamivudine, and nevirapine (62.1%). Median ART duration was 350 days (11.6 months). Significant improvements in clinical and immunologic status were noted after 12 months of therapy. ART switches occurred in 701 (54.5%) patients. The cumulative incidence of ART switch at 12 months was 78.4%. Concurrent ART-related toxicities (40.6%) and tuberculosis treatment interactions (28.1%) were the most frequent reasons for ART switch. Baseline AIDS symptoms (hazard rate [HR] = 1.59, 95% confidence interval [CI]: 1.28 to 1.98; $P < 0.01$) and a CD4 count $\leq$100 cells/mm^3 (HR = 1.20, CI: 1.01 to 1.43; $P = 0.04$) were independent predictors of ART switch. ART-related clinical toxicity occurred in 341 (26.5%) patients. Peripheral neuropathy was reported most frequently (20.7%). A CD4 count $\leq$100 cells/mm^3 was an independent predictor of clinical toxicity.

Conclusions: Excellent clinical and immunologic responses to ART were observed in this urban Kenyan population; however, frequent switches in ART among medication classes because of toxicity or drug interactions may limit the durability of these responses.

Key Words: antiretroviral therapy, HIV infection, resource-limited settings

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HIV remains the leading cause of mortality in sub-Saharan Africa. Until recently, antiretroviral therapy (ART) for the treatment of HIV was largely inaccessible because of high cost, inadequate infrastructure, and concerns about suboptimal adherence.[1,2] The availability of ART has now become more widespread as a result of increased funding and international attention to the epidemic. In June 2005, the Joint United Nations/World Health Organization Program on HIV/AIDS (UNAIDS/WHO) estimated that approximately 950,000 HIV-infected individuals were receiving ART in the developing world, with 500,000 of them in sub-Saharan Africa. The benefits of treatment in these settings have been well documented, with several studies reporting similar, and often superior, clinical and immunologic outcomes compared with those in developed countries.[3,4]

Ensuring that HIV treatment is efficacious, safe, accessible, and affordable is important for successful and sustainable ART programs in resource-limited settings. Monitoring and prevention of ART-related toxicities and failure are crucial, because access to alternative ART regimens is limited. In addition, providing adequate patient follow-up, drug supply, and monitoring while on ART minimizes interruptions in therapy and reduces chances for development of viral resistance.

Despite the numerous studies on the efficacy of ART in resource-limited settings,[3,5–7] only a few have addressed issues affecting long-term sustainability of HIV programs such as patient adherence to follow-up and durability and tolerability of first-line ART regimens.

This observational study investigated outcomes of ART in HIV-infected adults in an urban resource-limited setting, focusing on ART management, toxicity, and clinical follow-up.

METHODS

Study Site

Saint Mary's Mission Hospital, located in Nairobi, Kenya, has an HIV program offering basic HIV care to local residents since 2002. Since 2003, funding for much of the HIV program costs, including ART, has been provided by the President's Emergency Plan for AIDS Relief (PEPFAR). A small fee is required for clinic visits. This study was approved by the Northwestern University Institutional Review Board and the Executive Committee of Saint Mary's Mission Hospital.

Study Population

All HIV-infected patients presenting to the outpatient clinic were eligible for enrollment into the program. Pregnant

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patients were the only group excluded. This analysis includes all HIV-infected patients naive to ART enrolled between September 2004 and August 2006 who subsequently initiated ART through this program. Patients were required to be adults (at least 18 years of age) and to have at least 1 follow-up visit while on ART.

Patient Follow-Up and Assessment

HIV care was provided at the outpatient clinic by 6 physicians trained in the management of HIV and HIV-related infections. Treatment algorithms consistent with WHO guidelines for care of HIV-infected patients were developed locally and followed throughout the study period.[8] First-line ART regimens consisted of stavudine or zidovudine, lamivudine, and efavirenz or nevirapine. Second-line drugs available included tenofovir and lopinavir/ritonavir. Single-drug substitutions and regimen changes for toxicity, failure, or other reasons were managed according to WHO guidelines and at the discretion of the patient's physician. Patients visited the clinic monthly after enrollment for clinical evaluation, refills of ART, and medication adherence counseling. Laboratory tests, including a complete blood cell count, creatinine level, liver function tests, and CD4 cell count, were performed at baseline and at approximately 3-month intervals. Baseline tuberculosis (TB) testing, including a chest radiograph (CXR) and sputum processing for acid-fast bacilli, was performed on all patients at enrollment.

Data Collection

Physicians completed standardized forms capturing demographic, clinical, laboratory, and therapeutic information at baseline and at each patient visit. A separate form was filled out if a patient was withdrawn from the program for any reason. The data collected by the physicians were then entered into a secure computerized database designed solely for the purposes of patient data collection and analysis. Unique patient identifiers were used. The database was updated daily by dedicated data entry clerks trained to use a prospective data collection instrument. Weekly quality assurance checks of the database were performed by those who entered the data and the data manager to ensure data accuracy. This included auditing a preselected sample of charts to ensure that data on the forms matched those entered into the computer and performing checks for missing data. On a quarterly basis, interim inspection and analyses of the data were performed. Any missing pertinent data noticed during the data analyses or quality assurance issues were brought to the attention of the data manager and the physicians.

Outcomes

The main immunologic outcome observed was the mean change in CD4 cell count over time. To evaluate clinical response, each patient was assessed for HIV/AIDS-related symptoms or a new opportunistic infection (OI) at every clinic visit by the clinician. HIV/AIDS-related symptoms were defined as any symptom that was considered to be related to the patient's underlying HIV disease (ie, symptoms of pneumonia, weight loss) but that could not be definitively diagnosed as an OI. A new OI was defined as the diagnosis of an AIDS-defining infection in a patient on ART who had never been diagnosed with a prior OI. The proportion of patients exhibiting HIV/AIDS-related symptoms or developing an OI was then followed over time. HIV/AIDS-related symptoms were included as an outcome measure in addition to the presence of an OI, given the insufficient resources for diagnostic testing of OIs in this setting. A switch in therapy occurred if the ART regimen recorded at follow-up was different from the regimen initially started. Any individual drug substitution or regimen change was considered a switch. Dose reductions, however, were not considered an ART switch. The time of the first switch defined the time of reaching the outcome. If the physician recorded a symptom during a clinic visit believed to be attributable to ART, a toxicity event was considered to have occurred. Patients were determined to have laboratory-based liver toxicity if the serum glutamic oxaloacetic transaminase (SGOT) level was found to be greater than 5 times the upper limit of normal at any time on ART in a patient without a previous recording at this level. Loss to follow-up was defined as missed clinic visits and failure to collect ART refills for $\geq$3 months. Deaths were recorded based on physician or family notification on the discontinuation or "off-program" form. Official records such as death certificates were not usually available.

Statistical Analysis

Univariate comparisons of continuous and dichotomous outcomes were performed using Wilcoxon rank sum and χ^2 tests, respectively. Cox proportion hazard regression modeling was performed to determine multivariate predictors of each outcome. Covariates used in this modeling were age, baseline CD4 cell count, baseline HIV/AIDS-related symptoms, presence of an OI before ART, gender, and marital status. Separate Cox proportion hazard analyses were performed with the model, including switching therapy as a time-dependent covariate along with the variables listed previously. The Kaplan-Meier method was used to generate survival curves of the outcomes. Cumulative incidences of the outcomes were calculated at 6 and 12 months. For this analysis, the number of outcome events was divided by the total number of patients who were at risk for the entire time period. Statistical significance was defined as a P value <0.05 using 2-sided tests. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics and Antiretroviral Initiation

Between September 2004 and August 2006, 2922 HIV-infected patients were enrolled into the HIV program. A total of 1286 patients were included in this analysis. Patients were excluded for the following reasons: 80 patients were already on ART at program enrollment, 1473 patients had never initiated ART or had no follow-up on therapy, and 83 patients were $<$18 years old.

The median age was 36 years, 760 (59.1%) patients were female, and 893 (77.6%) had a baseline CD4 count $\leq$200 cells/mm^3 (Table 1). Five hundred twenty-one (40.5%)

TABLE 1. Baseline Characteristics of Study Population

Baseline Characteristics	No. Patients (%) (Total N = 1286)
Demographics	
Female	760 (59.1%)
Median age (range)	36 (18–70)
Married	706 (54.9%)
Location Nairobi	783 (60.9%)
HIV infection	
Median baseline CD4 count, cells/mm^3 (range)	121 (10–1308)
CD4 count ≤200 cells/mm^3	893 (77.6%)
CD4 count ≤100 cells/mm^3	471 (40.9%)
Median baseline weight, kg (range)	57 (5–106)
Baseline weight ≤50 kg	301 (27.3%)
Median baseline hemoglobin, g/dL (range)	10.4 (3.1–18.2)
Active/recent OI	521 (40.5%)
TB	441 (34.3%)
AIDS symptoms	498 (41.9%)
Antiretrovirals	
NNRTI-containing initial antiretroviral regimen	1272 (98.9%)
Individual regimens	
Stavudine + lamvivudine + nevirapine	798 (62.1%)
Stavudine + lamivudine + efavirenz	472 (36.7%)
Stavudine + lamivudine + lopinavir/ritonavir	9 (0.7%)
Tenofovir + lamivudine + lopinavir/ritonavir	5 (0.4%)
Zidovudine + lamivudine + nevirapine	2 (0.2%)

patients had an active or previous OI, and 441 (34.3%) patients had a history of TB before starting ART.

Nearly all the patients (98.9%) started a nonnucleoside reverse transcriptase inhibitor (NNRTI)–based ART regimen. Ninety-nine percent of patients initiated ART because of a CD4 count ≤200 cells/mm^3 or because they had symptomatic AIDS or an OI.

Clinical and Immunologic Outcomes

Significant improvements in clinical and immunologic outcomes were observed in patients on ART (Figs. 1, 2). The mean increases in CD4 count from baseline were 169, 208, and 210 cells/mm^3 at 6, 12, and 18 months on therapy, respectively ($P < 0.01$). Mean increases in weight at 6, 12, and 18 months on therapy were 4.5, 6.5, and 4.9 kg, respectively ($P < 0.01$). Hemoglobin levels increased a mean of 1.7 g/dL after 12 months on therapy and 3.0 g/dL after 18 months on therapy ($P < 0.01$). HIV/AIDS-related symptoms deceased significantly in patients over time on ART from a prevalence of 41.9% at baseline to 0.5% and 0.8% at 12 and 18 months, respectively ($P < 0.01$). Development of a new OI occurred in 180 (14.0%) patients after a median time on therapy of 50 days (range: 4–532 days). The cumulative incidences of new OIs were 17.1% at 6 months and 24.8% at 12 months (Fig. 3). The OIs reported in order of frequency were pulmonary TB (159 [46.2%]), candidiasis (54 [15.7%]), wasting (33 [9.6%]), extrapulmonary TB (19 [5.5%]), recurrent pneumonia (14 [4.1%]), Kaposi sarcoma (15 [4.4%]), herpes zoster (17 [4.9%]), chronic diarrhea (11 [3.2%]), HIV-related encephalopathy (6 [1.7%]), cryptococcal meningitis (4 [1.2%]), herpes simplex with chronic ulcer (4 [1.2%]), *Pneumocystis carinii* pneumonia (3 [0.9%]), lymphoma (3 [0.9%]), cervical cancer (1 [0.3%]), and other OI (1 [0.3%]). The only significant predictor of the development of a new OI was having a baseline CD4 count ≤100 cells/mm^3 (hazard rate [HR] = 1.49, 95% confidence interval [CI]: 1.06 to 2.09; $P = 0.02$). Only 14 deaths (1.1%), 13 of which occurred in men, were recorded during the current clinical follow-up period. The deaths occurred after a median of 139 days (range: 13–377 days).

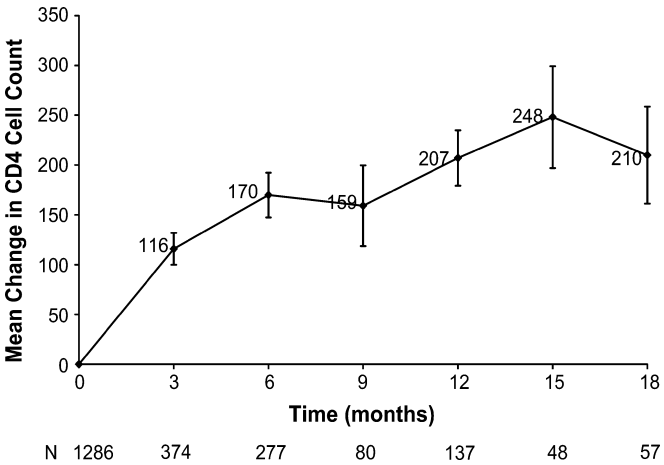

FIGURE 1. Mean change in CD4 cell count over time on ART.

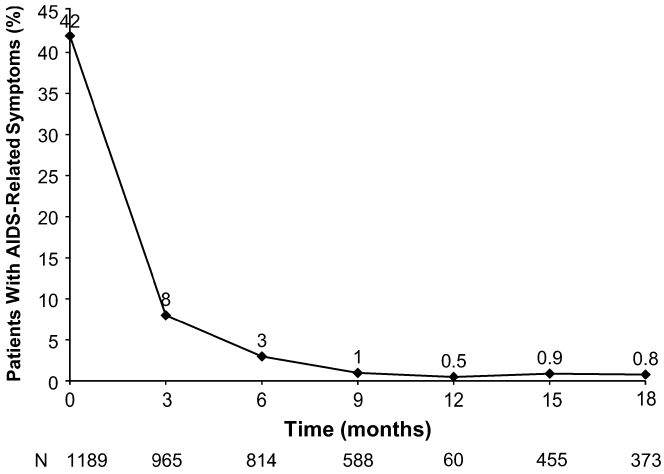

FIGURE 2. Prevalence of HIV/AIDS-related symptoms over time on ART.

Antiretroviral Duration and Modifications

The median duration of ART in this analysis was 350 days (11.6 months; range: 1–722 days). Nine hundred three patients were treated with ART for 6 months, 617 patients for 12 months, and 347 patients for 18 months.

More than half of the patients (701 [54.5%]) switched at least 1 drug of their initial ART regimen during the observation period. The cumulative incidences of ART switch were 63.1% and 78.4% at 6 and 12 months, respectively. Most switches were within an ART class, with only 90 (7.0%)

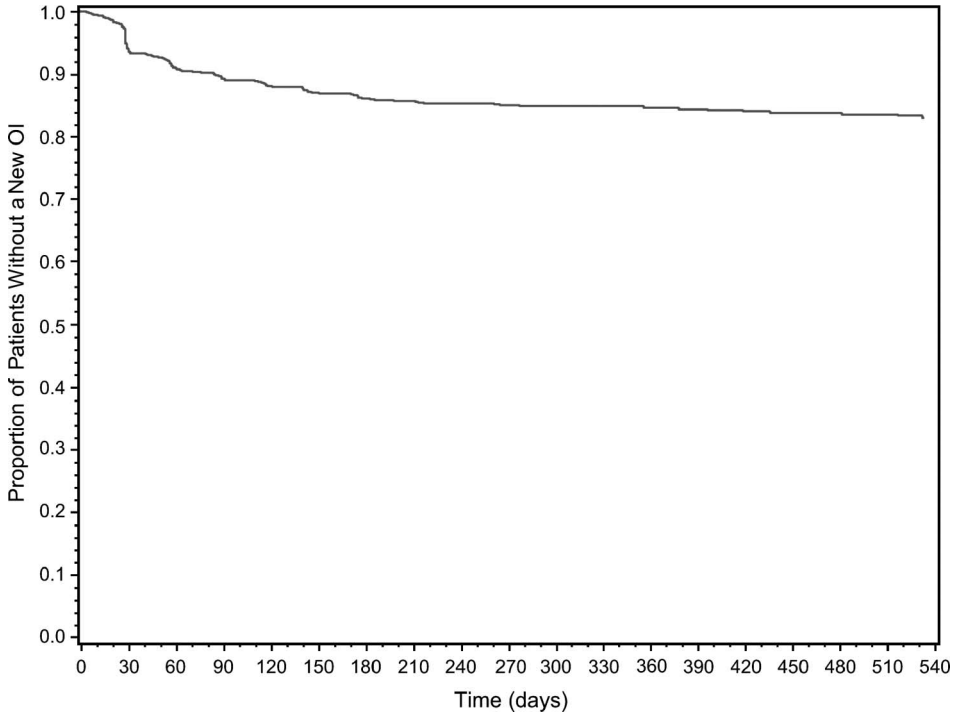

FIGURE 3. Probability of remaining free of a new OI.

patients switching to a different class of ART. Toxicity was the cause of ART switch in 40.6% of the patients with a reported reason (Table 2).

Among those who switched any ART, the median time on therapy before switching was 80 days (range: 5–623 days). Significant independent predictors of switching any ART were age ≥40 years (HR = 1.27, 95% CI: 1.07 to 1.51; $P < 0.01$), baseline CD4 count ≤100 cells/mm^3 (HR = 1.20, 95% CI: 1.01 to 1.43; $P = 0.04$; Fig. 4), AIDS-related symptoms at baseline (HR = 1.59, 95% CI: 1.28 to 1.98; $P < 0.01$), and male gender (HR = 1.20, 95% CI: 1.00 to 1.43; $P = 0.047$).

With any ART switch as a time-dependent covariate, switching therapy was an independent predictor of the subsequent development of a new OI (HR = 12.19, 95% CI: 8.16 to 18.21; $P < 0.01$), clinical toxicity (HR = 1.95, 95% CI: 1.50 to 2.52; $P < 0.01$), or withdrawal from the program (HR = 1.48, 95% CI: 1.18 to 1.85; $P < 0.01$).

Among those who switched ART class, the median time on therapy was 224 days (range: 6–630 days). There were no significant predictors of ARV class switch.

TABLE 2. Reported Reasons for First Antiretroviral Switch*

Switch Reason	Number (%)
Toxicity	117 (40.6%)
Immunologic or clinical failure	53 (18.4%)
TB medication interaction	81 (28.1%)
Antiretroviral supply limitation	23 (8.0%)
Other (compliance, planned or unplanned pregnancy)	14 (4.9%)
Total	288 (100.0%)

*Not all patients who switched had a reported reason.

Antiretroviral Clinical Toxicity

Three hundred ninety-nine episodes of clinical ART toxicity were reported among 341 (26.5%) patients on therapy (Table 3). The cumulative incidences of clinical toxicity were 24.5% at 6 months and 44.1% at 12 months. Neuropathy was the highest reported toxicity, accounting for 66.7% of observed toxicities (20.7% overall). The median time to development of clinical toxicity was 158 days (range: 0–682 days). The only significant predictors of development of clinical toxicity were baseline CD4 count ≤100 cells/mm^3 (HR = 1.3, 95% CI: 1.001 to 1.70; $P = 0.049$) and age >40 years (HR = 1.37, 95% CI: 1.05 to 1.78; $P = 0.02$). Baseline weight ≤50 kg was not found to be a significant predictor of clinical toxicity. ART-related laboratory liver toxicity was not observed in any patients.

Program Withdrawal

Five hundred eleven (39.7%) patients who started ART withdrew from the HIV program after a median of 118 days (range: 1–706 days). The cumulative incidences of program withdrawal were 30.4% and 42.7% at 6 and 12 months, respectively. Four hundred thirty-five (85.1%) patients who withdrew from the program were lost to follow-up, 63 (12.3%) patients transferred to another HIV treatment program, and 13 (2.6%) patients left for other reasons. Significant predictors of program withdrawal were the presence of AIDS symptoms at baseline (HR = 1.59, 95% CI: 1.24 to 2.03; $P < 0.01$) and being unmarried (HR = 1.44, 95% CI: 1.17 to 1.78; $P < 0.01$).

DISCUSSION

Overall, findings in this observational study showed excellent clinical and immunologic outcomes from a large-scale

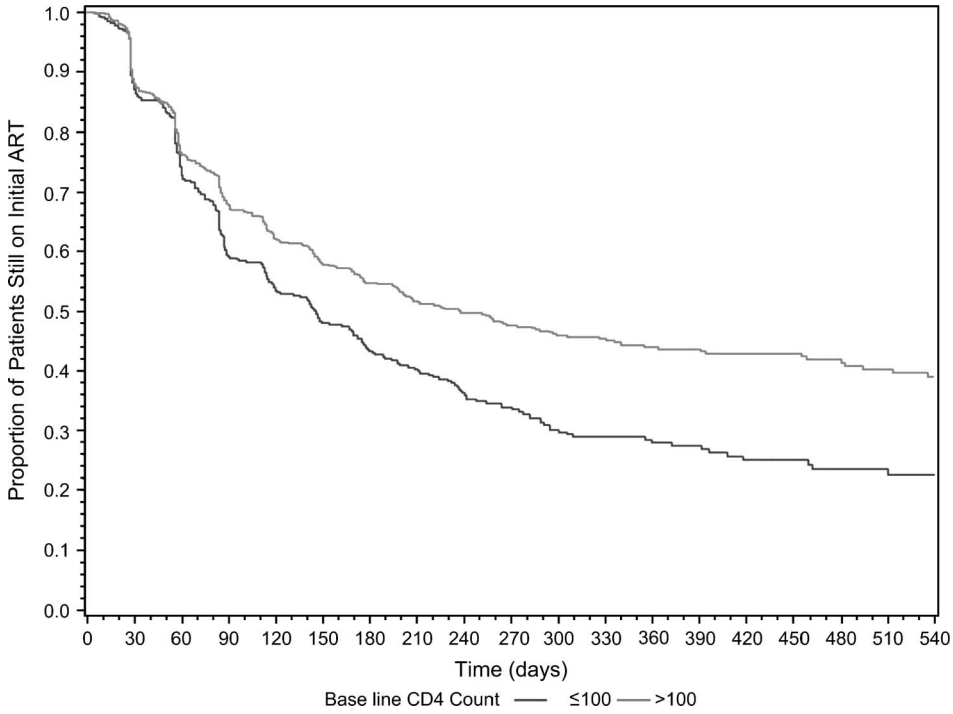

FIGURE 4. Probability of remaining free of a first-line antiretroviral switch stratified by baseline CD4 count (≤ or >100 cells/mm^3).

HIV treatment program in a resource-limited setting; however, we observed some issues with respect to ART management and program withdrawal that may compromise the long-term sustainability of these responses.

ART in this cohort resulted in robust clinical responses driving the prevalence of symptomatic HIV infection to less than 1% at the end of follow-up. Mean increases in CD4 cell count, hemoglobin, and weight were similar to those observed in other cohorts in resource-limited settings.[2] New OIs developed in 14% of individuals on ART, with cumulative incidence rates at 12 months similar to those in a recently published study from Botswana by Wester et al.[7] The relatively short period between ART initiation and new OI development (median = 50 days on ART) suggests that OIs were a result of immune reconstitution or, in the case of TB, relatively insensitive baseline screening methods. Additionally, OIs may have developed before the full effects of ART could be attained in this immunocompromised population.

TABLE 3. Reported Clinical Toxicities

Clinical Toxicity	Number (% of Total N = 1286)
Peripheral neuropathy	266 (20.7%)
Rash	47 (3.7%)
Central nervous symptomatology (eg, headache, vivid dreams)	37 (2.9%)
Gastrointestinal (nausea, vomiting, diarrhea, anorexia)	13 (1.0%)
Lipodystrophy	28 (2.2%)
Jaundice/hepatitis	3 (0.2%)
Other	5 (0.4%)
Total	399* in 341 (26.5%) patients

*Some patients experienced more than 1 toxicity.

ART toxicity, interactions, and supply were important factors affecting the durability of initial ART regimens in this cohort. Notably, among those who had been on therapy for at least 12 months, the cumulative incidence of patients switching any ART drug was 78.4%. This amount of ART switching exceeds rates observed among other cohorts in resource-limited settings.[1,4–7,9] ART switches were also found to occur after a short time on therapy (median = 2.7 months). These findings were not surprising, considering that the most common reasons for ART switch were toxicity and TB medication interaction. Among this cohort, lower baseline CD4 cell counts were observed to be a predictor of clinical toxicity, the leading cause of ART switch. Presumably, individuals who were immunocompromised at baseline were more susceptible to clinical toxicities and more likely to switch therapy for this reason. Alternatively, ongoing HIV symptoms (eg, HIV-related neuropathy) may have been misdiagnosed as toxicities. Stricter definitions of clinical toxicities and closer monitoring of these individuals may be useful to assist in diagnostic overlap and reduce potentially unnecessary ART switches in these instances.

A concerning observation was the finding that switching ART was a significant independent predictor for the development of subsequent toxicity, a new OI, or withdrawal from the program. Potentially, toxicity persisted after switching therapy, or the patients were at risk for recurrent toxicities. Other studies support this result by showing that patients making switches to first-line ART for toxicity are at significantly increased risk of recurrent toxicity.[10] The predilection for a new OI suggests clinical failure in those

who switched ART, possibly as a result of resistance to subsequent ART regimens. Viral load testing and resistance testing in select cases could have assisted in making this determination, but these studies were not available in this setting.

Modifiable reasons for ART switch were supply limitation and TB medication interactions, both of which are reasons for ART switch in other studies.[6,11,12] ART supply limitation resulted in ART switch in 8% of patients. Interruptions to ART supply are not uncommon in resource-limited settings and may result from delayed shipments, ART manufacturer stock-outs, and inaccurate ART quantification estimates.

Concurrent use of TB medications, including rifampin, resulted in a number of switches to ART between nevirapine and efavirenz. The use of rifabutin in TB regimens may be an approach to treat both infections simultaneously because it has fewer pharmacologic interactions with antiretrovirals than rifampin.[13] Another alternative would be the use of triple-nucleoside ART regimens during TB treatment.[14]

Among other cohorts from resource-limited settings, ART switch attributable to failure occurred in as many as 14% of individuals on first-line ART.[12] Rates of ART switch for clinical or immunologic failure were similarly low in this cohort; however, there are some limitations to this observation. Underestimations of ART failure could have occurred because the physicians only had clinical and immunologic information to determine ART success.

Overall, the number of clinical toxicity events was moderate and similar in frequency to that of other cohorts from resource-limited settings.[11,15–17] Stavudine-associated peripheral neuropathy was the most frequent toxicity in our cohort and accounted for a substantial proportion of ART switches. Peripheral neuropathy is seen with high frequency in resource-limited settings, and its association with stavudine use has been well documented.[7,11,15,16] In 2 recent observational studies assessing ART-related toxicity in Cameroon and India, neuropathy was the leading cause of ART switch.[15,16] Neuropathy is more frequent in immunocompromised individuals and can occur independent of stavudine use as well. Another stavudine-related toxicity that occurred at a relatively low frequency in our cohort was lipodystrophy. There are increasing reports of lipodystrophy related to nucleoside use from cohorts in resource-limited settings.[19,20] These findings have important implications, especially given the frequency of ART modifications that have occurred because of lipodystrophy in developed countries.[21]

Other important ART-related toxicities observed in our cohort were rash and hepatotoxicity related to NNRTI use. Rash occurred in approximately 3.7% of patients, which is a lower rate than that observed among other cohorts in resource-limited settings[22,23] but similar to that observed in clinical trials with nevirapine in developed countries.[24] Laboratory-based hepatotoxicity was not observed in any of these patients. This is notable, given the many patients treated with nevirapine in this cohort. Hepatotoxicity associated with nevirapine use has been reported with varying frequency in other studies of ART-related toxicity in resource-limited settings.[25]

A large number of patients in our cohort were lost to follow-up after a relatively short time on ART. Baseline AIDS symptoms was an independent predictor of program withdrawal. This large loss to follow-up rate is not unique to our cohort and reflects the difficulties in tracking patients in resource-limited settings with passive reporting systems.[4,26–30] Many patients switched to other programs in which ART was provided free of charge, suggesting that the nominal clinic fee per visit played a role in patients who withdrew. Costs associated with ART have been associated with poor adherence, interruptions or discontinuation of ART, loss to follow-up, and poorer outcomes in several other studies.[12,27,30–34]

There were significant limitations to our study. Because this study was observational, not all patients were equal in terms of time in the program, on therapy, and on follow-up. Selection bias could not be avoided, particularly because we limited our analysis to adult patients who were in the program for at least 1 follow-up visit. The primary data for diagnosis and ART management were determined through physician reporting in a clinical record; therefore, there were potential inaccuracies or omissions in these data. Additionally, no other source of records (ie, dispensing records) was used for comparison. Despite these limitations, this study is one of the larger cohorts of HIV-infected patients on ART in resource-limited settings.

In conclusion, our findings support the ongoing feasibility of ART rollout in resource-limited settings. Nevertheless, efforts should be made to maximize ART durability by minimizing the number of patients switching therapy or withdrawing from these important programs. These endeavors may include the use of more tolerable first-line ART, ensuring unlimited ART provision, and consideration of alternative treatment options in the management of TB coinfection. Because of the likelihood of stavudine toxicity affecting initial ART regimen durability in this setting, future HIV programs should reconsider using stavudine as part of front-line therapy.

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REFERENCES

1. Laurent C, Ngom Gueye NF, Ndour CT, et al, for the ANRS 1215/1290 Study Group. Long-term benefits of highly active antiretroviral therapy in Senegalese HIV-1–infected adults. *J Acquir Immune Defic Syndr*. 2005; 38:14–17.
2. Desclaux A, Ciss M, Taverne B, et al. Access to antiretroviral drugs and AIDS management in Senegal. *AIDS*. 2003;17(Suppl):S95–S101.
3. Akileswaran C, Lurie MN, Flanigan TP, et al. Lessons learned from use of highly active antiretroviral therapy in Africa. *Clin Infect Dis*. 2005;4: 376–385.

4. Braitstein P, Brinkhof MW, Dabis F, et al. Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration; Antiretroviral Therapy Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet*. 2006;367:817–824.
5. Coetzee D, Hildebrand K, Boulle A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS*. 2004;18:887–895.
6. Severe P, Leger P, Charles M, et al. Antiretroviral therapy in a thousand patients with AIDS in Haiti. *N Engl J Med*. 2005;353:2325–2334.
7. Wester CW, Kim S, Bussmann H, et al. Initial response to highly active antiretroviral therapy in HIV-1C–infected adults in a public sector treatment program in Botswana. *J Acquir Immune Defic Syndr*. 2005;40: 336–343.
8. World Health Organization. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. Geneva, Switzerland: World Health Organization; 2003.
9. Wanchu A, Pareek S, Bambery P, et al. Adverse drug reactions to generic ART in resource-constrained settings: implication for scaling-up therapy [abstract 562]. Presented at: 13th Conference on Retroviruses and Opportunistic Infections; 2006; Denver.
10. Dieleman JP, Jambroes M, Gyssens IC, et al for the ATHENA Study Group. Determinants of recurrent toxicity-driven switches of highly active antiretroviral therapy. The ATHENA cohort. *AIDS*. 2002;16:737–745.
11. Forna F, Liechty C, Solberg P, et al. Early clinical toxicity to nonnucleoside reverse transcriptase inhibitor-based HAART in a home-based AIDS care program in rural Uganda [abstract 142]. Presented at: 13th Conference on Retroviruses and Opportunistic Infections; 2006; Denver.
12. Kumarasamy N, Vallabhaneni S, Cecelia AJ, et al. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. *J Acquir Immune Defic Syndr*. 2006;41: 53–58.
13. Finch CK, Chrisman CR, Baciewicz AM, et al. Rifampin and rifabutin drug interactions: an update. *Arch Intern Med*. 2002;162:985–992.
14. DART Virology Group and Trial Team. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa. *AIDS*. 2006;20:1391–1399.
15. Laurent C, Kouanfack C, Koulla-Shiro S, et al. Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial. *Lancet*. 2004;364:29–34.
16. Kumarasamy N, Solomon S, Chaguturu SK, et al. The safety, tolerability and effectiveness of generic antiretroviral drug regimens for HIV-infected patients in south India. *AIDS*. 2003;17:2267–2269.
17. Pujari SN, Patel AK, Naik E, et al. Effectiveness of generic fixed-dose combination of highly active antiretroviral therapy for treatment of HIV infection in India. *J Acquir Immune Defic Syndr*. 2004;37:1566–1569.
18. Deleted in proof.
19. Pujari SN, Dravid A, Naik E, et al. Lipodystrophy and dyslipidemia among patients taking first-line, World Health Organization-recommended highly active antiretroviral therapy regimens in western India. *J Acquir Immune Defic Syndr*. 2005;39:199–202.
20. Van Griensven J, Mushi T, Ubarijoro S, et al. Prevalence of lipodystrophy after 1 year of WHO first line ART in Kigali, Rwanda [abstract 560a]. Presented at: 13th Conference on Retroviruses and Opportunistic Infections; 2006; Denver.
21. Garcia-Benayas T, Blanco F, de la Cruz JJ, et al. Replacing stavudine by abacavir reduces lactate levels and may improve lipoatrophy. *AIDS*. 2003; 17:921–924.
22. Jack C, Lalloo U, Abdool Karim Q, et al. A pilot study of once-daily antiretroviral therapy integrated with tuberculosis directly observed therapy in a resource-limited setting. *J Acquir Immune Defic Syndr*. 2004;36:929–934.
23. Karcher H, Moses A, Weide AL, et al. Evaluation of antiretroviral treatment in Fort Portal, western Uganda [abstract B12706]. Presented at: 15th International AIDS Conference; 2004; Bangkok.
24. van Leth F, Phanuphak P, Ruxrungtham K, et al, for the 2NN Study Team. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. 2004;363:1253–1263.
25. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV infected subjects. *J Infect Dis*. 2005;191:825–829.
26. Wools-Kaloustian K, Kimaiyo S, Diero L, et al. Viability and effectiveness of large-scale HIV treatment initiatives in sub-Saharan Africa: experience from western Kenya. *AIDS*. 2006;20:41–48.
27. Kabugo C, Bahendeka S, Mwebaze R, et al. Long-term experience providing antiretroviral drugs in a fee-for-service HIV clinic in Uganda: evidence of extended virologic and $CD4^+$ cell count responses. *J Acquir Immune Defic Syndr*. 2005;38:578–583.
28. Djomand G, Roels T, Ellerbrock T, et al. Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Cote d'Ivoire. *AIDS*. 2003;17(Suppl):S5–S15.
29. van Oosterhout JJ, Bodasing N, Kumwenda JJ, et al. Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi. *Trop Med Int Health*. 2005;10:464–470.
30. 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.
31. Ivers LC, Kendrick D, Doucette K. Efficacy of antiretroviral therapy programs in resource poor settings: a meta-analysis of the published literature. *Clin Infect Dis*. 2005;41:217–224.
32. Bisson G, Strom J, Gross R, et al. Lack of health insurance is associated with lower response to highly active antiretroviral therapy in treatment naive patients at a large private clinic in Botswana [abstract 26]. Presented at: 12th Conference on Retroviruses and Opportunistic Infections; 2005; Boston.
33. 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):S103–S108.
34. Hosseinipour MC, Kanyama C, Nkhalamba T, et al. Safety and efficacy of d4T/3TC/NVP among HIV positive adults in Lilongwe, Malawi [abstract TuPeB4522]. Presented at: 15th International AIDS Conference; 2004; Bangkok.