Sustainability of First-Line Antiretroviral Regimens: Findings From a Large HIV Treatment Program in Western Kenya

Paula Braitstein, PhD,†‡§ Paul Ayuo, MMed, MBChB,†‡ Ann Mwangi, PhD (cand),†‡§¶ Kara Wools-Kaloustian, MD,*†‡ Beverly Musick, MSc,*‡ Abraham Siika, MMed, MBChB, MS,*†‡ and Sylvester Kimaiyo, MMed, MBChB†‡*

Objective: To describe first change or discontinuation in combination antiretroviral treatment (cART) among previously treatment naive, HIV-infected adults in a resource-constrained setting.

Methods: The United States Agency for International Development–Academic Model Providing Access to Healthcare Partnership has enrolled >90,000 HIV-infected patients at 18 clinics throughout western Kenya. Patients in this analysis were aged ≥18 years, previously antiretroviral treatment naive, and initiated to cART between January 2006 and November 2007, with at least 1 follow-up visit. A treatment change or discontinuation was defined as change of regimen including single drug substitutions or a complete halting of cART.

Results: There were 14,162 patients eligible for analysis and 10,313 person-years of follow-up, of whom 1376 changed or stopped their cART. Among these, 859 (62%) changed their regimen (including 514 patients who had a single drug substitution) and 517 (38%) completely discontinued cART. The overall incidence rate (IR) of cART changes or stops per 100 person-years was 13.3 [95% confidence interval (CI): 12.7–14.1]. The incidence was much higher in the first year of post-cART initiation (IR: 25.0, 95% CI: 23.6–26.3) compared with the second year (IR: 2.4, 95% CI: 2.0–2.8). The most commonly cited reason was toxicity (46%). In multivariate regression, individuals were more likely to discontinue cART if they were World Health Organization stage III/IV [adjusted hazard ratio (AHR): 1.37, 95% CI: 1.11–1.69] or were receiving a zidovudine-containing regimen (AHR: 4.44, 95% CI: 3.35–5.88). Individuals were more likely to change their regimen if they were aged ≥38 years (AHR: 1.44, 95% CI: 1.23–1.69), had to travel more than 1 hour to clinic (AHR: 1.34, 95% CI: 1.15–1.57), had a CD4 at cART initiation ≤111 cells/mm^3 (AHR: 1.51, 95% CI: 1.29–1.77), or had been receiving a zidovudine-containing regimen (AHR: 3.73, 95% CI: 2.81–4.95). Those attending urban clinics and those receiving stavudine-containing regimens were less likely to experience either a discontinuation or a change of their cART.

Conclusions: These data suggest a moderate incidence of cART changes and discontinuations among this large population of adults in western Kenya. Mostly occurring within 12 months of cART initiation, and primarily due to toxicity, older individuals, those with more advanced disease, and those using zidovudine are at higher risk of experiencing a change or a discontinuation in their cART.

Key Words: antiretroviral, Africa, treatment durability, adverse effects, treatment failure

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INTRODUCTION

The clinical benefits of combination antiretroviral treatment (cART) have been demonstrated in multiple clinical settings, including in regions with an inadequate health care infrastructure and a high prevalence of comorbid infections such as tuberculosis.[1,2] Over the past 5 years, the international community has made substantial strides in rolling-out cART to individuals in resource-constrained settings such that 31% of those currently in need of treatment for HIV/AIDS are now receiving it.[3] Clinical and operational questions surrounding the roll-out of antiretrovirals have moved from the debate about whether to provide cART to the specifics of how to further scale-up the distribution of treatment, and how to maximize the long-term tolerability and sustainability of antiretroviral regimens.

Treatment regimens are limited in resource-constrained settings and affordable alternatives for individuals experiencing toxicity or treatment failure are few. Reports from these settings indicate that between 17%[4,5] and 78%[6] of patients switch or discontinue their antiretrovirals. These figures raise many questions for health care providers and planners, such as, when are patients most likely to have to change or stop their cART? How many patients have to stop or change their cART due to toxicity? Which patients should be more closely monitored to prevent changes or discontinuations in their antiretroviral treatment?

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From the *Department of Medicine, Indiana University, School of Medicine, Indianapolis, IN; †Department of Medicine, Moi University, School of Medicine, Eldoret, Kenya; ‡USAID-Academic Model Providing Access to Healthcare (AMPATH) Partnership, Eldoret, Kenya; §Regenstrief Institute, Indianapolis, IN; and ¶Department of Biostatistics, Brown University, RI.

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Correspondence to: Paula Braitstein, PhD, Indiana University School of Medicine, 1001 West 10th Street, OPW-M200, Indianapolis, IN 46202 (e-mail: pbraitstein@yahoo.com).

The primary objectives of this study were therefore to (1) calculate the incidence of first change or discontinuation of cART among adults receiving first-line therapy in a large HIV treatment program in western Kenya; (2) to describe the timing of the change or discontinuation; (3) to describe clinician-stated reasons for the change or discontinuations; and (4) to identify sociodemographic and clinical risk factors associated with experiencing a treatment change or discontinuation.

METHODS

Study Design

This was a retrospective study using prospectively collected clinical data. This study was approved by the Indiana University School of Medicine Institutional Review Board and the Moi University School of Medicine Institutional Review and Ethics Committee.

The Program

The Academic Model Providing Access to Healthcare (AMPATH) program was initiated in 2001 as a joint partnership between Moi University School of Medicine, the Indiana University School of Medicine, and the Moi Teaching and Referral Hospital. The United States Agency for International Development (USAID)–AMPATH Partnership was initiated in 2004 when AMPATH received ongoing funding through USAID and the United States Presidential Emergency Plan for AIDS Relief. The initial goal of AMPATH was to establish an HIV care system to serve the needs of both urban and rural patients and to assess the barriers to and outcomes of antiretroviral therapy. Details of the development of this program have been described in detail elsewhere.[7] The first urban and rural HIV clinics were opened in November 2001. Since then, the program has enrolled more than 90,000 HIV-infected adults and children in 18 Ministry of Health facilities and numerous satellite clinics in western Kenya (data for satellite clinics are incorporated into their "parent" clinic). All HIV- and tuberculosis-related care and treatment are provided free at the point of care for patients through AMPATH and the Kenyan National Leprosy, Tuberculosis, and Lung Disease Program.

Clinical Procedures

The HIV clinical care protocols used by the USAID–AMPATH Partnership are consistent with those recommended by the World Health Organization (WHO) and the Kenya Ministry of Health's National AIDS and STI Control Program. These protocols have been described in detail elsewhere.[2] Briefly, patients receiving cART are seen by the clinician (clinical officer or physician) 2 weeks after initiating treatment, and then monthly thereafter. Those who have not initiated cART return every 1–3 months depending on their clinical status and comorbidities. All patients newly initiated on cART who miss a scheduled clinic visit trigger an outreach attempt through telephone contact or home visit by trained peers within 24 hours of the patient's missed visit. The goals of these contacts are to determine the patient's vital status and encourage return to the treatment program if they have not transferred their care to another program.

During the period these data were collected, laboratory monitoring included semiannual CD4 counts and plasma viral loads for patients with evidence of immunologic failure (CD4 decline of >25% from peak) or inadequate response to cART. Liver and renal function tests, and complete blood counts, were conducted annually on all patients, unless symptoms provoked a clinician to request an off-cycle test. Lactate was unavailable during the period of the study.

Data Collection

Clinicians complete standardized forms capturing demographic, clinical, and pharmacologic information at each patient visit. These data are then hand entered into the AMPATH Medical Record System, a secure computerized database designed for clinical management, with data entry validated by random review of 10% of the forms entered.[8] At the time of registration, patients are provided with a unique identifying number. For this study, all data were stripped of identifying information before analysis.

Study Population

Patients were included in this analysis if they were aged 18 years or over at the time of cART initiation, were previously treatment naive, and had at least 1 day of follow-up. Women who had ever or who were taking antiretrovirals for the prevention of mother to child transmission were excluded from the analysis. Patients in this analysis initiated cART between January 1, 2006 and November 3, 2007.

Outcomes and Variables

The primary endpoint for this analysis was the first regimen change (including single drug substitutions) or complete discontinuation of cART. Dose modifications were not included.

Reasons for cART changes or discontinuations were based on those documented by the clinician. The categories on the encounter forms are treatment failure (defined as a confirmed CD4 decline of 25% from peak, failure of CD4 cell count to rise or failure to rise to above 200 cells/mm^3 after 12 months of treatment), toxicity, and other. Due to the large number of reasons defined as "other" we conducted a retrospective chart review to identify other important reasons for the treatment change or discontinuation. The most common "other" reasons were initiation of tuberculosis treatment and poor patient adherence to cART.

Independent variables were both sociodemographic and clinical in nature. We hypothesized that the following variables could be associated as either predictive variables or confounders with the probability of having a treatment change or discontinuation: age at treatment initiation (analyzed as a continuous variable and then dichotomized at the population median), sex, whether the patient was attending an urban or a rural clinic, the time required for the patient to travel to the clinic (1 hour or less vs. more than 1 hour), WHO stage at cART initiation (stage III/IV vs. I/II), CD4 count at cART initiation (defined as the CD4 count closest to the date of cART initiation but no more than 180 days before or 7 days after cART initiation, measured as both a continuous, and dichotomized at the median), and whether patients received

a stavudine-, zidovudine-, or nevirapine-containing regimen (yes/no).

Analysis

Normally and nonnormally distributed categorical and dichotomous variables were analyzed using the chi-square and Kruskal–Wallis tests, respectively. The medians and interquartile ranges of continuous variables were analyzed with the Wilcoxon Rank Sum test.

The Kaplan–Meier method was used to estimate incidence of and time to treatment change or stop. Incidence rates (IRs) are presented per 100 person-years (PY) of follow-up. Patients were censored at the time of the event, or at their last clinic visit if they did not have an event or were lost to follow-up. Cox Proportional Hazards was used to calculate unadjusted hazard ratios, adjusted hazard ratios (AHRs), and 95% confidence intervals (CIs). Separate models were fit excluding all antiretroviral variables, and then separately for the use of stavudine-, zidovudine-, and nevirapine-containing regimens because of overlap among them, particularly with nevirapine. Variables were entered into the final model if they were statistically significant at an alpha of 0.05 or if they were believed to be potential confounders (age, sex). Models were stratified according to whether the patient experienced a complete stop in treatment or a change in regimen.

All P values are 2 sided. All analyses were done with STATA Version 10/SE (College Station, TX).

RESULTS

There were 15,300 patients aged 18 years and over who were previously treatment naive and initiated cART during the study period. Of these, 1138 (7%) had 0 days of follow-up and were subsequently excluded. There were 14,162 patients with at least 1 day of follow-up, who together contributed 10,313 PY of follow-up. This population was predominantly women (n = 8894; 63%), with a mean age at cART initiation of 38.9 years (median 37.8). The median CD4 count at cART initiation was 114 cells/mm^3 (interquartile range [IQR] 52–180). The median follow-up time from cART initiation was 252 days (mean 265). During the study period, 1590 (11%) individuals became lost to follow-up and were subsequently censored.

There were 1376 individuals who had a treatment change or discontinuation, of whom 859 (62%) changed and 517 (38%) completely discontinued their cART. Of those who changed their regimen, 514 (60%) had a single drug substitution. The majority of all changes and discontinuations (91%) occurred during the first year on cART. Overall, the incidence of either treatment change or discontinuation was 13.3 per 100 PY, and was much higher in the first year post-cART initiation: 24.9 (23.6–26.4) per 100 PY, compared with 2.4 (2.0–2.8) in their second year. The incidence of discontinuing cART was 5.0 (4.6–5.5) per 100 PY, whereas the incidence of changing cART was 8.3 (7.8–8.9) per 100 PY.

The most common reason for the change or discontinuation in cART was toxicity (46%) (Fig. 1). Poor adherence (18%) and tuberculosis induction therapy (13%) were other frequently cited reasons. Antiretroviral treatment failure only accounted for 3% of the stated reasons for discontinuing or changing cART. Upon stratification of discontinuations and changes, the most common reasons for discontinuing were poor adherence (48%) and toxicity (23%), whereas the most common reasons for changing were toxicity (59%) and initiation of tuberculosis treatment (19%).

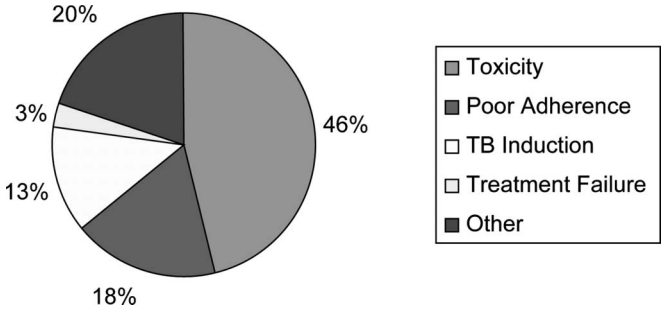

FIGURE 1. Physician-stated reasons for cART change or discontinuation.

As summarized in Table 1, those who experienced a treatment change or discontinuation were different in their sociodemographic and clinical profile at baseline compared with those who continued on their initial regimens. Those who had a treatment change or discontinuation were slightly older (median 39.9 vs. 37.7 years, $P < 0.001$), more likely to attend a rural clinic (58% vs. 47%, $P < 0.001$), and somewhat more likely to be WHO stage III/IV (63% vs. 60%, $P = 0.012$). Those who had a change or stop had a slightly lower median CD4 count at cART initiation (101 vs. 115 cells/mm^3, $P < 0.001$), and were proportionately more likely to be receiving a stavudine-containing regimen (88% vs. 83%, $P < 0.001$).

In multivariate Cox regression (Table 2), those aged 38 years and over (AHR 1.22, 95% CI: 1.08–1.38), having to travel more than 1 hour to reach clinic (AHR 1.28, 95% CI: 1.13–1.44), having a baseline CD4 of ≤111 cells/mm^3 (AHR: 1.29, 95% CI: 1.14–1.46), WHO clinical stage III/IV at cART initiation (AHR 1.22, 95% CI: 1.08–1.39), and individuals who initiated cART with zidovudine (AHR 4.04, 95% CI: 3.31–4.93) were more likely to experience a change or a discontinuation of their cART. There was no statistical association between the use of nevirapine-containing regimens and treatment changes or discontinuations.

Individuals who discontinued their regimen were more likely to be WHO clinical stage III/IV and more likely to have been receiving a zidovudine-containing regimen. In contrast, individuals who changed their regimens were older, had a lower baseline CD4 count, and were more likely to have been receiving zidovudine. Those attending urban clinics and those receiving stavudine were less likely to discontinue or change their cART.

DISCUSSION

These results indicate a moderate rate of switching or discontinuing cART in this resource-constrained setting, at 13%, with the risk of the initial discontinuation or change in treatment being highest in the first-year post-cART initiation. Toxicity was the most commonly cited reason, particularly for

TABLE 1. Baseline Sociodemographics and Clinical Characteristics of Those Who Experienced a Change or Discontinuation of Their CART Compared With Those Who Did Not (N = 14,162)

Variable	Discontinued or Changed cART (n = 1376), n (%)	Sustained cART (n = 12,786), n (%)	*P*
Sex			
Male	506 (37)	4762 (37)	0.731
Female	870 (63)	8024 (63)	
Missing	0	0	
Age at start of cART			
Median (IQR)	39.9 (33.1–46.4)	37.7 (31.8–44.4)	<0.001
Missing	7 (0.5)	28 (0.2)	
Clinic location			
Urban	576 (42)	6792 (53)	<0.001
Rural	800 (58)	5994 (47)	
Missing	0	0	
Time to reach clinic			
≤1 h	660 (52)	6909 (58)	<0.001
>1 h	610 (48)	5022 (42)	
Missing	106 (7.8)	855 (6.7)	
WHO clinical stage at start of cART			
I/II	430 (37)	4310 (40)	0.012
III/IV	747 (63)	6383 (60)	
Missing	199 (14.5)	2093 (16.4)	
CD4 at start of cART			
Median (IQR)	101 (43–174)	115 (53–181)	<0.001
Missing	167 (12.1)	1603 (12.5)	
Stavudine			
Yes	1212 (88)	10,410 (83)	<0.001
No	161 (1)	2129 (17)	
Missing	3 (0.2)	247 (1.9)	
Zidovudine			
Yes	158 (11)	2062 (16)	<0.001
No	1215 (89)	10,477 (84)	
Missing	3 (0.2)	247 (1.9)	
Nevirapine			
Yes	1155 (84)	10.478 (84)	0.595
No	218 (16)	2061 (16)	
Missing	3 (0.2)	247 (1.9)	

changing treatment. Concern about poor adherence was the most common reason for a treatment discontinuation, followed by toxicity, whereas treatment failure was an uncommon reason for either discontinuing or changing cART. Baseline risk factors for either discontinuing or changing cART were the use of zidovudine and more advanced HIV disease at cART initiation.

These data highlight several important issues for clinicians and program planners.

First is the necessity of managing toxicities early and proactively. We hypothesize that the strong association between changing and discontinuing treatment with zidovudine is related to the significant risk of anemia that accompanies this drug.[9] Further research is needed to identify individuals who are at risk for zidovudine-induced anemia in sub-Saharan Africa, where the background prevalences of malnutrition and malaria are high. The strong negative association between stavudine and discontinuations and changes in treatment may be related to a lower side effect profile than zidovudine, but may also be related to the program's inability to test for the most life threatening toxicity associated with stavudine, lactic acidosis. This issue requires more research as mortality and losses to follow-up among patients receiving stavudine may be higher if this hypothesis is true. It is crucial to note that stavudine is much less widely used in high-income settings because of its toxicity profile[10] and as such it is imperative that careful attention be paid to the toxicities experienced by patients in sub-Saharan Africa and that improved laboratory monitoring be made available to programs that are reliant on this drug in their primary regimen. In addition, international efforts to make safe and affordable alternatives available should be pursued. In our study, there was no independent association between the use of nevirapine and changes or discontinuations in cART. We believe this is due to its being a generally well-tolerated medicine.[11]

These data also suggest that although treatment failure may become more common as time on cART accrues, clinicians are actively engaging their patients in discussions about adherence, and stopping their patients cART proactively if adherence is believed to be poor. Such practices may account for treatment failure being the least likely reason for discontinuing or switching antiretrovirals within our cohort.

Our findings are consistent with other programs who reported a prevalence of treatment discontinuations and changes of 20% and who found that adverse effects were the most common reasons for them.[12] However, they do not support the findings of another study from Kenya which reported that 78% of their patients stopped or switched their cART treatment by 12-months postinitiation.[6] Despite this difference between the 2 studies, the reasons identified for these outcomes were similar.[6] Patients in the mutlicenter Euro-Sida cohort had an incidence of discontinuing treatment of 6% (including nonnaive patients). This rate is lower than that found in our study, but Euro-Sida used a more conservative definition (discontinuing cART for a period of at least 3 months).[13]

There are several key strengths to our study. The first being that we examined cART changes and discontinuations independently and combined, and therefore the results provide a comprehensive picture of cART sustainability in our setting. The second is that the USAID–AMPATH Partnership is a large clinical population, covering much of western Kenya, in both urban and rural settings. As such our sample provided ample statistical power to assess factors associated with regimen changes and discontinuations, and is more broadly generalizable to other sub-Saharan Africa settings. Third, by calculating incidence during different periods after treatment initiation and identifying causes and risk factors, we have been able to provide greater insight to clinicians and health care planners for optimizing therapeutic options. Fourth, as AMPATH services are free to patients, there is no confounding due to fee for service care structures. Fifth, because there were no

TABLE 2. AHRs and 95% CIs for Discontinuing And/or Changing CART

	Discontinued or Changed cART AHR (95% CI)	Discontinued cART AHR (95% CI)	Changed cART AHR (95% CI)
Age ≥38 vs. <38 years	1.22 (1.08–1.38)	0.96 (0.79–1.16)	1.44 (1.23–1.69)
Sex (male vs. female)	0.99 (0.87–1.12)	1.07 (0.87–1.31)	0.94 (0.80–1.10)
Time travel to clinic (>1 h vs. ≤ 1 h)	1.28 (1.13–1.44)	1.18 (0.98–1.44)	1.34 (1.15–1.57)
CD4 at cART (≤111 cells/mm^3 vs. >111 cells/mm^3)	1.29 (1.14–1.46)	1.01 (0.83–1.23)	1.51 (1.29–1.77)
WHO clinical stage (III/IV vs. I/II)	1.22 (1.08–1.39)	1.37 (1.11–1.69)	1.14 (0.97–1.34)
Clinic location (urban vs. rural)	0.64 (0.55–0.72)	0.61 (0.50–0.75)	0.65 (0.56–0.77)
*Stavudine regimen (yes vs. no)	0.27 (0.22–0.33)	0.23 (0.18–0.30)	0.31 (0.24–0.42)
*Zidovudine regimen (yes vs. no)	4.04 (3.31–4.93)	4.44 (3.35–5.88)	3.73 (2.81–4.95)
*Nevirapine regimen (yes vs. no)	0.89 (0.74–1.06)	0.74 (0.57–0.97)	1.02 (0.80–1.29)

*Three separate models were constructed for each of the 3 regimen variables. The AHRs and CIs for the other variables in the model remained nearly identical in each one and so are only presented once.

pharmacy stock-outs during the study period (or since), we can confidently say our findings are not due to disruptions in the supply chain.

Limitations to this analysis may include random misclassification due to clinician error in recording. Second, despite chart reviews, a relatively large proportion of "other" reasons for a treatment change or discontinuation remain unknown because the clinician did not record the reason. A third limitation is that despite large patient numbers, the amount of follow-up time is relatively limited, preventing us from examining more closely the impact of treatment failure. Fourth, it is of note that all individuals who started cART and who never kept any follow-up visit, and those who became lost to follow-up, could technically be classified as a treatment discontinuation but were excluded/censored (respectively) from our analysis. Therefore, our presentation of the incidence of treatment discontinuation may be viewed as an underestimate. Fifth, whether a patient stops or changes their cART will depend to some extent on the availability of alternatives. Although not a direct limitation of our analysis, this does affect the generalizability of our findings to other centers, in other periods.

In conclusion, our data regarding the rates of and risk factors for experiencing a change or discontinuation in cART have several implications for the delivery of HIV care and treatment in resource-constrained settings. One, toxicities need to be managed early and proactively to support patients in sustaining their first-line regimen for as long as possible. Two, initiating cART earlier in the HIV disease process and bringing guidelines for cART in resource-constrained settings closer to the present guidelines in the United States,[10] before the development of other comorbid conditions such as tuberculosis,[14] may reduce possible drug interactions and consequently, toxicity burden. Three, clinicians are actively withdrawing their patients from their antiretroviral treatment in an effort to prevent the development of resistance in them. The effect of these treatment discontinuations on the outcomes of patients in the future will need to be closely evaluated. In addition, identifying the outcomes of patients lost to follow-up, and how these may relate to the toxicities associated with cART and stavudine in particular, will be an important next research question. Taken together, these data give reasons to be optimistic about the durability of potent cART in sub-Saharan Africa, but the continued scale-up of treatment must balance rapidity, with individual patient support. Increased treatment options, together with more frequent laboratory monitoring focusing on both possible toxicities and viral load, will greatly assist clinicians and patients in making the best evidence-based clinical decisions possible. Thus, will be maximized the sustainability of first-line ART regimens for HIV-infected patients in resource-constrained settings.

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