

Impact of Prior HAART Use on Clinical Outcomes in a Large Kenyan HIV Treatment Program[§]

Michael H. Chung^{*,1}, Alison L. Drake², Barbra A. Richardson^{3,4}, Ashok Reddy¹, Joan Thiga⁵, Samah R. Sakr⁵, James N. Kiarie⁶, Paul Yowakim⁵ and Grace C. John-Stewart^{1,2}

Departments of ¹Medicine, ²Epidemiology, and ³Biostatistics, University of Washington, Seattle, USA; ⁴Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, USA; ⁵Coptic Hospital, Nairobi, Kenya; ⁶Department of Obstetrics and Gynaecology, University of Nairobi, Kenya

Abstract: *Background:* HIV treatment programs in Africa typically approach all enrolling patients uniformly. Growing numbers of patients are antiretroviral experienced. Defining patients on the basis of antiretroviral experience may inform enrollment practices, particularly if medical outcomes differ.

Methods: Baseline and follow-up measures (CD4, weight change, and survival) were compared in a retrospective analysis between antiretroviral-naïve (ARV-N) and antiretroviral experience (ARV-E) patients enrolled at the Coptic Hope Center for Infectious Diseases in Nairobi, Kenya and followed between January 2004 and August 2006.

Results: 1,307 ARV-N and 962 ARV-E patients receiving highly active antiretroviral therapy (HAART) were followed for median of 9 months (interquartile range: 4-16 months). Compared to ARV-N, ARV-E had substantially higher CD4 count (median cells/mm³, 193 versus 95, $P < 0.001$) and weight (median kg, 62 versus 57, $P < 0.001$) at baseline, and lower rates of change in CD4 (-9.2 cells/mm³/month; 95% CI, -11.4 – -7.0) and weight (-0.24 kg/month; 95% CI, -0.35 – -0.14) over 12 months. Mortality was significantly higher in ARV-N than ARV-E ($P = 0.001$).

Conclusions: ARV-E patients form a growing group that differs significantly from ARV-N patients and requires a distinct approach from ARV-N clients. Systematic approaches to streamline care of ARV-E patients may allow focused attention on early ARV-N clients whose mortality risks are substantially higher.

Keywords: Africa, HAART, HIV-1, clinic flow, experience, mortality.

INTRODUCTION

In the last five years, there has been a substantial increase in the number of HIV-infected patients receiving highly active antiretroviral therapy (HAART) in resource-limited settings [1]. Concurrent with exponential enrollment rates has been the demonstration of clinical success; CD4 counts have risen and mortality rates have dropped dramatically [2-5]. Considerable funding to expand HIV treatment clinics in sub-Saharan Africa has grown with an aim to increase comprehensive antiretroviral coverage for many.

The challenge for many antiretroviral treatment programs, however, has been how to sustain delivery of quality medical care to an ever increasing number and diversity of HIV-infected patients [6]. As global treatment efforts mature and more people receive life-long treatment for this chronic disease, progressively more patients who are already receiving HAART are switching to new programs for care, either to evaluate alternative programs, or to receive care closer to home [7]. Clinics must therefore care not only for new patients, but an increasing number who have

received HAART previously and are antiretroviral-experienced. Thus, this group of patients is forming an increasing portion of the clinic population whose outcomes and needs may differ significantly from antiretroviral-naïve patients who have been the focus of the majority of studies citing clinical treatment success in resource-limited settings [8-10].

Similarly, most treatment centers in resource-limited settings like sub-Saharan Africa have established clinic systems and protocols that assume HIV patients are naïve to antiretroviral care. Substantial effort is expended on counseling and initiating HAART despite overwhelming numbers of patients and limited administrative and physical infrastructures. Understanding the impact of prior HAART experience on clinical outcomes and initial presentation may therefore inform methods to optimize provision of care at these sites. Differing outcomes may inform implementation of new public health strategies that handle the treatment and flow of patients through resource-constrained clinics based on antiretroviral treatment experience.

This study describes antiretroviral-experienced patients continuing HAART (ARV-E) at the Coptic Hope Center for Infectious Diseases, a large HIV treatment clinic in Nairobi, Kenya, and compares them to antiretroviral-naïve patients initiating HAART at the clinic (ARV-N).

MATERIALS AND METHODS

Coptic Hope Center for Infectious Diseases

Institutional Review Boards (IRB) at the University of Washington and Kenyatta National Hospital (KNH)

*Address correspondence to this author at the Department of Medicine, University of Washington, Seattle, IARTP, Box 359909, Washington 98104, USA; Tel: 206-543-4278; Fax: 206-543-4818; E-mail: mhchung@u.washington.edu

[§]A Portion of this data was presented at the Infectious Diseases Society of America (IDSA) Conference in October 2006 in Toronto and published as oral abstract #689.

approved this study. The study was designed as a retrospective review of data from all adult patients enrolled at the Coptic Hope Center for Infectious Diseases in Nairobi, Kenya between January 2004 and August 2006. The Hope Center is a HIV clinic that offers free antiretroviral therapy, prophylaxis, and palliative care to any adult or child who is HIV-positive, regardless of prior HAART exposure or eligibility to receive HAART. Established in January 2004, the HIV clinic is administered by the Coptic Orthodox Mission in collaboration with the University of Washington. Services, supplies, and medications are supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through a cooperative agreement from the US Centers for Disease Control and Prevention (CDC). The Hope Center is an urban clinic that primarily serves patients residing in Nairobi, but includes those living outside the city and throughout Kenya.

Clinic Protocols

Patients enrolling at the Hope Center were confirmed HIV-positive by an Elisa HIV antibody test and had a baseline CD4 count. Those who met criteria for initiating HAART per Kenyan national guidelines were given antiretroviral medications. Antiretroviral medications were free for all patients after October 2004. Eligible HAART patients included those who had CD4 counts < 200 cells/mm³ and/or had World Health Organization (WHO) Clinical Stage IV disease. Those who did not meet criteria for HAART initiation, or were reluctant to begin therapy, were offered medical care, counseling, and free CD4 count testing every 6 months.

The first-line antiretroviral regimen prescribed by the Hope Center was lamivudine, stavudine, and nevirapine formulated as a fixed-dose generic combination pill taken twice a day. Other free antiretroviral medications offered by the clinic included zidovudine, didanosine, tenofovir, abacavir, efavirenz, and lopinavir/ritonavir. These additional medications replaced the first-line formulary based on medical need, drug-drug interactions, adverse effects, or antiretroviral failure. Patients on HAART were required to visit a clinician at least once every three months, and to pick up antiretroviral medications from the pharmacist every one to two months. Throughout the period of the study there were no interruptions in the supply of antiretroviral medications.

Mortality was determined by hospital medical records, or phone call from the social worker to friends and family designated by the patient to be emergency contacts. If a patient reported receiving HAART at any point prior to their first screening visit at the Hope Center, and continued to receive antiretroviral medications, then they were defined as ARV-E. ARV-N patients were those patients that had never been exposed to HAART prior to enrollment at the Hope Center, were eligible to receive HAART, and initiated antiretroviral therapy at the clinic. Those who had previously been given antiretroviral medications to prevent mother-to-child transmission of HIV were also classified as ARV-N.

Data Collection

Data were gathered from patients using paper forms that were electronically scanned into a computer database using

Cardiff TeleForm (Vista, CA). Information from every patient visit was recorded on these forms by clinicians, nurses, counselors, social workers, and nutritionists. A data management team based at the Hope Center verified and cleaned the data upon scanning. Pharmacy visits and patient medication information were recorded at the time of patient visit by pharmacists using a Microsoft Access database system (Seattle, WA). This live pharmacy database system tracked drug inventory, monitored prescribing practices, and recorded patient attendance.

Statistical Methods

The Mann-Whitney U test was used to compare distributions of continuous variables, while the Mantel-Haenszel and Pearson chi-square tests were used to compare dichotomous and categorical variables respectively. The effect of antiretroviral treatment status at baseline on CD4 count and weight over time was evaluated using linear mixed effects models with random intercepts, random slopes, and an unstructured covariance matrix. A locally weighted scatterplot smoother was applied to scatterplots of CD4 and weight. The Kaplan-Meier method was used to analyze time to death; differences in curves were assessed using the log-rank test.

Multivariate Cox regression models were developed to explore survival further. Models included age, gender, and WHO stage as *a priori* covariates. Exploratory models including income and education in addition to the *a priori* covariates were also developed. A test of proportional hazards was performed on the basis of Schoenfeld residuals to assure that the assumption of proportional hazards was met in the time to death analyses.

Statistical analyses were conducted using SPSS 14.0 (Chicago, IL) and STATA 10.0 (College Station, TX).

RESULTS

Study Population

A total of 4,411 adult patients enrolled at the Coptic Hope Center for Infectious Diseases between January 1, 2004 and August 31, 2006 (Fig. 1). Of these, 1,054 (24%) had previously received HAART, 3,275 (74%) had never received HAART, and 82 (2%) had an unknown antiretroviral history at baseline. Nine hundred and sixty two antiretroviral-experienced patients (91%) continued care at the Hope Center and received HAART (ARV-E). Among the 3,275 patients who had not received HAART previously, 2,837 (87%) were evaluated by clinical and laboratory parameters: 1,687 (59%) were eligible to begin HAART and 1,150 (41%) were ineligible. Of those who were eligible, 1,307 (77%) initiated HAART at the Hope Center (ARV-N) and 380 (23%) did not.

Characteristics of ARV-E vs ARV-N

Comparing ARV-E and ARV-N revealed significant differences in demographic and behavioral characteristics between the two patient subgroups. ARV-E were older (median years, 39 versus 36, $P < 0.001$), and were more likely to have > 8 years of primary education (78% versus 64%, $P < 0.001$), and to earn > \$150 per month (21% versus 16%, $P < 0.001$) than ARV-N (Table 1). ARV-E were more

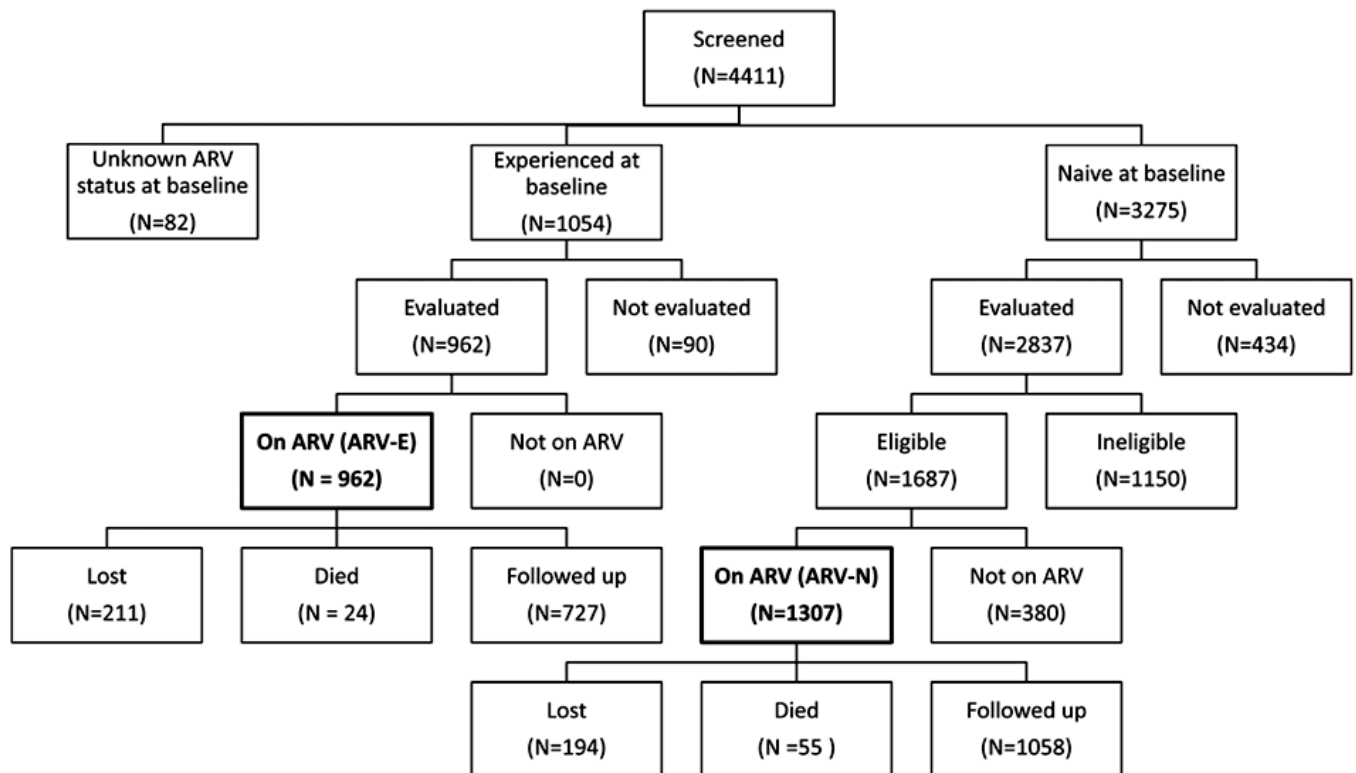


Fig. (1). Flowchart of adult patients enrolling at the Coptic Hope Center for Infectious Diseases between January 2004 and August 2006.

likely than ARV-N to have revealed their HIV serostatus to another person [odds ratio (OR), 2.21; 95% confidence interval (CI), 1.63-3.00] and have family members on antiretroviral treatment (OR, 3.36; 95% CI, 2.46-4.58).

Clinical characteristics and outcomes differed significantly between ARV-E and ARV-N. Median time to initiating HAART after enrollment was significantly shorter among ARV-E compared to ARV-N (median days, 0 versus 34, $P < 0.001$) (Table 1). At baseline, CD4 count (median cells/mm³, 193 versus 95, $P < 0.001$) was significantly higher among ARV-E than ARV-N. The rate of change in CD4 count over time differed between the two groups and the difference persisted over 12 months. The average change in CD4 count per month was 9.2 cells/mm³ lower among ARV-E than ARV-N (95% CI, -11.4 – -7.0) (Fig. 2). At 12 months after enrollment, the median CD4 count of ARV-E was 246 cells/mm³ compared to 203 cells/mm³ among ARV-N ($P < 0.001$).

Weight was also significantly different between ARV-E and ARV-N at enrollment with baseline weight higher among ARV-E compared to ARV-N (median kg, 62 versus 57, $P < 0.001$) (Table 1). Over 12 months of follow-up, ARV-E gained less weight compared to ARV-N with the average rate of change in weight being 0.24 kg lower per month among ARV-E than ARV-N (95% CI, -0.35 – -0.14) (Fig. 3). At 12 months after enrollment, median weight between the two arms were not significantly different (median kg, 64 versus 64, $P = 0.55$) (Table 1).

Mortality

Patients were followed for a median of 9 months [interquartile range (IQR), 4 – 16 months] after enrollment, and 2,005 person-years of observation were accrued.

The overall rate of death was 3.9 deaths per 100 person-years. Among ARV-N the death rate was 5.6 deaths per 100 person-years (95% CI, 4.8 – 6.4), while among ARV-E it was 2.3 deaths per 100 person-years (95% CI, 1.9 – 2.8). Twelve-month mortality risk was significantly higher in ARV-N than ARV-E in both univariate ($P = 0.001$) (Fig. 4) and multivariate analyses that included age, gender, income, education, and WHO stage (HR, 0.39; 95% CI, 0.21 – 0.72; $P = 0.003$). In a subset analysis, there was no significant difference in mortality between ARV-E and ARV-N ($P = 0.38$) in the first two months after enrollment, but between 2 and 12 months the probability of death among ARV-N was significantly greater than among ARV-E ($P = 0.0004$). At 12 months after enrollment, 5.6% (95% CI, 4.3 – 7.4%) of ARV-N had died compared to 2.3% (95% CI, 1.4 – 3.7%) of ARV-E.

DISCUSSION

In this study of patients attending a large HIV treatment clinic in Kenya, individuals who had used HAART prior to enrollment differed substantially from those who were HAART-naïve. Antiretroviral-experienced patients differed in sociodemographic characteristics from ARV-N patients, as well as in baseline CD4 counts, weight, and follow-up

Table 1. Demographic and Clinical Characteristics of ARV-E and ARV-N Patients Accessing Care Between January 2004 and August 2006

Characteristic	ARV-N (N=1307)		ARV-E (N=962)		ARV-N Versus ARV-E		
	N	Median (IQR) or N (%)	N	Median (IQR) or N (%)	OR	95% CI	p
Female	1307	794 (61%)	962	602 (63%)	1.08	(0.91 - 1.28)	0.38
Age	1307	36.1 (31.3 - 42.2)	962	39.1 (33.6 - 45.4)			<0.001
Married or cohabitating	1274	646 (51%)	782	386 (49%)	0.95	(0.79 - 1.13)	0.55
Education	1264		646				<0.001
< 5 years of primary		99 (8%)		25 (4%)			
5 - 8 years of primary		363 (29%)		117 (18%)			
> 8 years primary		802 (64%)		504 (78%)			
Monthly income \$	1247		699				<0.001
< \$70		549 (44%)		207 (30%)			
\$70 – \$150		505 (41%)		343 (49%)			
> \$150		193 (16%)		149 (21%)			
WHO Stage at baseline	1280		924				0.002
1		330 (26%)		264 (29%)			
2		265 (21%)		163 (18%)			
3		595 (47%)		397 (43%)			
4		90 (7%)		110 (11%)			
CD4							
CD4 (cells/mm ³) at baseline	1161	95 (46 - 154)	689	193 (100 - 324)			<0.001
CD4 (cells/mm ³) at 6 months	750	179 (120 - 264)	570	233 (136 - 359)			<0.001
CD4 (cells/mm ³) at 12 months	361	203 (144 - 304)	434	246 (158 - 386)			<0.001
Weight							
Weight (kg) at baseline	1290	57.3 (51.0 - 65.0)	930	62.0 (55.0 - 72.0)			<0.001
Weight (kg) at 6 months	965	59.5 (53.0 - 68.0)	697	62.4 (55.0 - 71.0)			<0.001
Weight (kg) at 12 months	519	64.0 (56.0 - 71.5)	541	64.0 (57.0 - 72.4)			0.55
Median time (days) to HAART	1307	34 (23 - 48)	962	0 (0 - 56)			<0.001
Revealed HIV serostatus	1141	918 (81%)	596	537 (90%)	2.21	(1.63- 3.00)	<0.001
Family member on HAART	1161	75 (7%)	611	115 (19%)	3.36	(2.46 - 4.58)	<0.001

changes in these parameters. In addition, ARV-E clients were more likely to survive over 12 months than antiretroviral-naïve patients. These results are not surprising given the efficacy of antiretroviral medications. However, current programs tend to approach all new clients in the same way – with standard adherence counseling sessions, scheduled visits and monitoring. Our study provides data regarding rates of CD4 change and weight change in ARV-E patients that contrasts with that in ARV-N. These data can be directly useful to clinicians and patients for forecasting typical course.

In addition, the mortality data provides support for targeted approaches based on antiretroviral experience – re-directing increased attention by the program to patients who are starting antiretrovirals for the first time by streamlining efforts for ARV-E clients entering the program. ARV-N patients had significantly lower CD4 counts at baseline

compared to ARV-E. At risk for opportunistic infections, ARV-N had higher probability of death than ARV-E, particularly in the first 6 months after enrollment, a finding consistent with other studies demonstrating early treatment mortality in resource-limited settings [11-13]. A contributing factor in early mortality among ARV-N may also have been a longer period of time to start HAART compared to ARV-E, many of whom were continued on their previous regimens without delay, and may indicate that adherence counseling protocols should be adapted to initiate HAART sooner [14, 15].

There are several recommendations for HIV clinics enrolling large numbers of HIV patients in resource-limited settings that may be drawn from this study. First, the same social support protocols for enrollment that apply to ARV-N patients may not be necessary for all ARV-E patients. ARV-E patients can be referred to these services only if indicated,

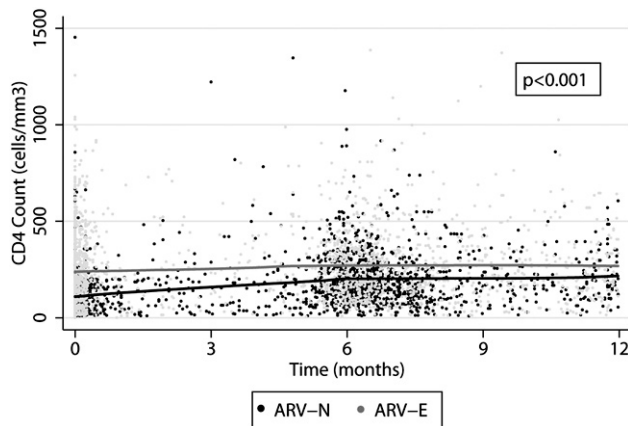


Fig. (2). Scatterplot of CD4 count over time by antiretroviral exposure at baseline. Curves represent locally weighted smoothed curves of CD4 count over time, by ARV status. Time = Time since enrollment.

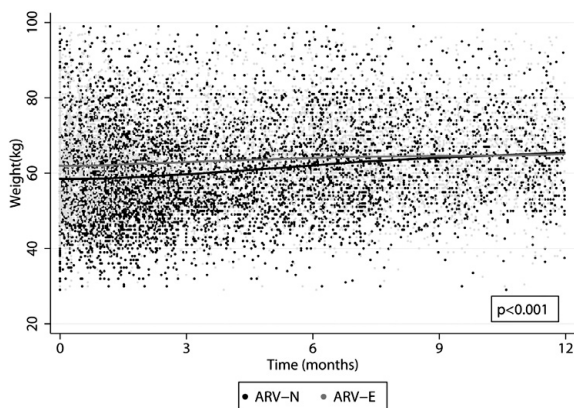


Fig. (3). Scatterplot of weight over time by antiretroviral exposure at baseline. Curves represent locally weighted smoothed curves of weight over time, by ARV status. Time = time since enrollment.

saving potential time and space. Second, after medical screening, stable ARV-E patients can be immediately assigned to a less rigorous follow-up schedule with extended time intervals between each visit. Decreasing the frequency of visits by ARV-E patients may relieve the burden on medical and pharmaceutical staff who can thereby concentrate their efforts on more fragile, ARV-N patients. Third, clinics should limit the time between enrollment and initiation of HAART, particularly in ARV-N patients who may be more vulnerable due to their immunocompromised state. Lastly, more links between treatment programs may avoid duplicated efforts and facilitate transfer of medical information to provide the best care for patients transitioning between clinics.

There are a few limitations to this study. It is not known why ARV-E transferred their care to the Hope Center and whether there was any interruption in their treatment during transfer. Some patients were followed-up for less than 4 months in the clinic. The study included antiretroviral-experienced patients from 2004, many of whom had received HAART because they could afford it, and this group of individuals may not represent antiretroviral-experienced patients who, in recent years, have received free medications. However, our findings on the association between antiretroviral experience and survival remained in multivariate analyses that included income and education, which suggests that they are a result of antiretroviral experience rather than sociodemographic differences between groups.

The successes described thus far in the treatment of HIV-infected patients living in resource-limited countries have focused primarily on adult patients never before exposed to antiretroviral medications. As treatment efforts mature, this study indicates that clinical achievements as measured by improvements in CD4 count and weight may be less profound. This study suggests that it is necessary to recognize that the initial honeymoon phase of treating large numbers of ARV-N patients in areas such as sub-Saharan

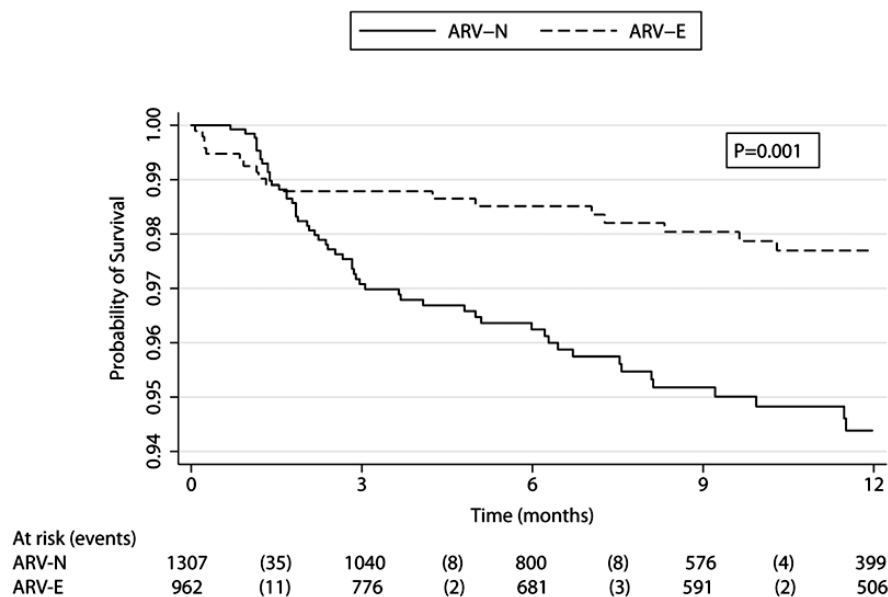


Fig. (4). Kaplan-Meier plot of survival by antiretroviral exposure at baseline. Time = time since enrollment.

Africa has passed and that population benefits may be less obvious as more patients reach a plateau in their response to treatment. Similarly, clinics will have to adjust to the new environment and respond to the fact that not only do millions of HIV-positive people require initiating antiretroviral medications for the first time, but millions are already receiving treatment. This is challenging since most clinics are guided by general medical protocols that apply to all patients, regardless of background, at enrollment.

Given the enormous number of patients who require antiretroviral treatment, the approach to HIV care in resource-limited settings has been on the scale of a public health endeavor. As a result, individual medical care has given way to delivering rapid, uniform care to many patients through generalized policies and public health guidelines. The limitation of a one-size-fits-all approach is that it cannot tailor strategies as well as intensive individualized systems that are usually more effective when treating chronic diseases such as HIV [16, 17]. The question becomes how to identify characteristics that may begin to help change clinic policies that can benefit groups of patients in a manner that is more specific to their needs.

This study demonstrates that it may be beneficial to identify patients at enrollment by prior HAART use. Patients defined by this term in this study bore similar clinical responses to treatment and counseling. Distinguishing between ARV-N and ARV-E patients at enrollment, antiretroviral treatment clinics in resource-limited settings may be able to cater their medical services accordingly and thereby improve overall medical outcomes.

ACKNOWLEDGEMENTS

We thank the research personnel, clinic staff, and data management teams in Nairobi, Kenya and Seattle, Washington; the Coptic Hope Center for Infectious Diseases for their participation and cooperation; and the Division of Obstetrics and Gynaecology at Kenyatta National Hospital for providing facilities for data analysis. Finally, we thank our patients whose courage continues to inspire us.

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report. None of the authors has a major conflict of interest in this study.

Michael H. Chung is supported by a K23 grant, National Institutes of Health (5K23AI065222-04). The Coptic Hope Center for Infectious Diseases is supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through a cooperative agreement (U62/CCU024512-04)

from the US Centers for Disease Control and Prevention (CDC).

REFERENCES

- [1] Katabira ET, Oelrichs RB. Scaling up antiretroviral treatment in resource-limited settings: successes and challenges. *AIDS* 2007; 21 (Suppl 4): S5-10.
- [2] Fairall LR, Bachmann MO, Louwagie GM, *et al.* Effectiveness of antiretroviral treatment in a South African program: a cohort study. *Arch Intern Med* 2008; 168: 86-93.
- [3] Severe P, Leger P, Charles M, *et al.* Antiretroviral therapy in a thousand patients with AIDS in Haiti. *N Engl J Med* 2005; 353: 2325-34.
- [4] Stringer JS, Zulu I, Levy J, *et al.* Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. *JAMA* 2006; 296: 782-93.
- [5] 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: 41-8.
- [6] Wagner G, Ryan G, Taylor S. Formative evaluation of antiretroviral therapy scale-up efficiency in sub-Saharan Africa. *AIDS Patient Care STDS* 2007; 21: 871-88.
- [7] Dalal RP, Macphail C, Mqhayi M, *et al.* Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in Johannesburg, South Africa. *J Acquir Immune Defic Syndr* 2008; 47: 101-7.
- [8] Coetzee D, Hildebrand K, Boulle A, *et al.* Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004; 18: 887-95.
- [9] 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: 217-24.
- [10] Sow PS, Otieno LF, Bissagnene E, *et al.* Implementation of an antiretroviral access program for HIV-1-infected individuals in resource-limited settings: clinical results from 4 African countries. *J Acquir Immune Defic Syndr* 2007; 44: 262-7.
- [11] Braitstein P, Brinkhof MW, Dabis F, *et al.* Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 2006; 367: 817-24.
- [12] Etard JF, Ndiaye I, Thierry-Mieg M, *et al.* Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. *AIDS* 2006; 20: 1181-9.
- [13] Marazzi MC, Liotta G, Germano P, *et al.* Excessive Early Mortality in the First Year of Treatment in HIV Type 1-Infected Patients Initiating Antiretroviral Therapy in Resource-Limited Settings. *AIDS Res Hum Retroviruses* 2008; 24(4): 555-60.
- [14] Lawn SD, Myer L, Orrell C, Bekker LG, Wood R. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS* 2005; 19: 2141-8.
- [15] Lawn SD, Myer L, Harling G, *et al.* Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation. *Clin Infect Dis* 2006; 43: 770-6.
- [16] Groves T, Wagner EH. High quality care for people with chronic diseases. *BMJ* 2005; 330: 609-10.
- [17] Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? *Eff Clin Pract* 1998; 1: 2-4.