Rapid Scale-up of Antiretroviral Therapy at Primary Care Sites in Zambia

Feasibility and Early Outcomes

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Context The Zambian Ministry of Health has scaled-up human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) care and treatment services at primary care clinics in Lusaka, using predominately nonphysician clinicians.

Objective To report on the feasibility and early outcomes of the program.

Design, Setting, and Patients Open cohort evaluation of antiretroviral-naive adults treated at 18 primary care facilities between April 26, 2004, and November 5, 2005. Data were entered in real time into an electronic patient tracking system.

Intervention Those meeting criteria for antiretroviral therapy (ART) received drugs according to Zambian national guidelines.

Main Outcome Measures Survival, regimen failure rates, and CD4 cell response.

Results We enrolled 21 755 adults into HIV care, and 16 198 (75%) started ART. Among those starting ART, 9864 (61%) were women. Of 15 866 patients with documented World Health Organization (WHO) staging, 11 573 (73%) were stage III or IV, and the mean (SD) entry CD4 cell count among the 15 336 patients with a baseline result was 143/μL (123/μL). Of 1142 patients receiving ART who died, 1120 had a reliable date of death. Of these patients, 792 (71%) died within 90 days of starting therapy (early mortality rate: 26 per 100 patient-years), and 328 (29%) died after 90 days (post-90-day mortality rate: 5.0 per 100 patient-years). In multivariable analysis, mortality was strongly associated with CD4 cell count between 50/μL and 199/μL (adjusted hazard ratio [AHR], 1.4; 95% confidence interval [CI], 1.0-2.0), CD4 cell count less than 50/μL (AHR, 2.2; 95% CI, 1.5-3.1), WHO stage III disease (AHR, 1.8; 95% CI, 1.3-2.4), WHO stage IV disease (AHR, 2.9; 95% CI, 2.0-4.3), low body mass index (<16; AHR,2.4; 95% CI, 1.8-3.2), severe anemia (<8.0 g/dL; AHR, 3.1; 95% CI, 2.3-4.0), and poor adherence to therapy (AHR, 2.9; 95% CI, 2.2-3.9). Of 11 714 patients at risk, 861 failed therapy by clinical criteria (rate, 13 per 100 patient-years). The mean (SD) CD4 cell count increase was 175/μL (174/μL) in 1361 of 1519 patients (90%) receiving treatment long enough to have a 12-month repeat.

Conclusion Massive scale-up of HIV and AIDS treatment services with good clinical outcomes is feasible in primary care settings in sub-Saharan Africa. Most mortality occurs early, suggesting that earlier diagnosis and treatment may improve outcomes.

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Zambia's population of 11.5 million persons is among the world's poorest and most severely affected by acquired immunodeficiency syndrome (AIDS).[1] Nationwide, 16% of adults are estimated to be infected with human immunodeficiency virus 1 (HIV 1), and in the capital city of Lusaka, 22% are infected. In 2003, more than 90 000 Zambians died of HIV disease.[2] Access to antiretroviral therapy (ART) in Zambia historically has been limited and available only through private medical practices to the country's affluent population. However, in early 2002, the Zambian Ministry of Health initiated pilot, public-

See also p 859.

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sector ART programs at the country's 2 largest hospitals. These programs filled to capacity almost immediately. It became evident to Zambian decision makers that the sheer magnitude of the nation's AIDS epidemic would far outstrip not only the number of available physicians but also the ability of the existing hospital system to cope. ART services would have to be delivered at the level of the primary health care center.

In May 2004, with funding from the US President's Emergency Plan for AIDS Relief (PEPFAR); the Global Fund to Fight AIDS, Tuberculosis, and Malaria[3]; and other sources, the Ministry of Health initiated ART services at 4 clinics in the Lusaka Urban District using mostly nonphysician clinicians.[4] At the time of program initiation, there was widespread uncertainty that complex, long-term HIV care could be delivered in a setting with so few physicians and so little physical and technical resources. Nevertheless, during the subsequent 18 months, the program expanded to 14 additional urban sites, with a goal of universal access to HIV care and treatment in Lusaka.[5] The roll out was accompanied by the elimination of all user fees for patients seeking AIDS care in the Lusaka District and by the provision of free antiretroviral drugs and laboratory tests.

Herein, we report our initial clinical experience with the rapid scale-up of HIV care and treatment in the urban primary health care setting of Lusaka. We detail survival, regimen failure rates, and CD4 cell response outcomes for more than 16 000 patients receiving ART.

METHODS

Support to Government Facilities

We formed a collaborative team comprising members of the Lusaka Urban Health District, the University Teaching Hospital, the Zambian National AIDS Council, and the Centre for Infectious Disease Research in Zambia (a local nongovernmental organization affiliated with the University of Alabama at Birmingham). Additional technical support was provided by the Elizabeth Glaser Pediatric AIDS Foundation, the University of California at San Francisco, and the local mission of the US Centers for Disease Control and Prevention.

PEPFAR-funded support to sites included the following: (1) training of nonphysician clinicians in HIV/AIDS care, including management of antiretroviral medications and opportunistic infections; (2) payment of overtime shifts to increase clinic staffing levels[6]; (3) support of pharmaceutical (including antiretroviral drugs) procurement, stock management, and forecasting; (4) improvement of laboratory capacity and securing of the Clinton Foundation reagent pricing[7]; (5) development and maintenance of an electronic patient tracking and outcomes monitoring system[8];(6) provision of clinical care quality oversight and continuing education; and (7) renovation of clinical and laboratory space. The Zambian Ministry of Health provided support for training, staffing, and antiretroviral drugs through its own budget and its various donor resources.

Clinical Care Protocols

Patients are accepted for evaluation by the HIV care and treatment program from any public or private source that can provide documentation of HIV infection. Those patients presenting with unknown serostatus are referred for laboratory testing. The vast majority of patients (>99%) evaluated are indigenous Zambians, but the program is open to all ethnicities and to citizens of other countries. Owing to shortages of physicians in Zambia and the region,[9] the majority of health care in Lusaka is delivered by clinical officers (analogous to US physician's assistants) and nurses.

To ensure a standard and complete approach under these staffing circumstances, we created form-driven patient care protocols that reflect national care standards. Each form is visit specific, and designed to guide clinical officers and nurses through standard work-ups and initial patient management. Rotating Zambian and expatriate physicians provide oversight, and they consult on complex patients and those patients believed by the nurses and clinical officers to be failing first-line therapy.

Initial evaluation includes medical history, physical examination, and CD4 cell count. A follow-up appointment occurs 1 to 2 weeks later, when laboratory results are reviewed and ART eligibility is determined according to Zambian national guidelines.[10] In the first months of the program, ART was initiated for individuals with either a CD4 cell count of less than 200/µL or for those in World Health Organization (WHO) stage III or IV. In 2005, these guidelines were revised to exclude ART eligibility for patients in WHO stage III with CD4 cell counts greater than 350/µL. All patients, whether starting ART or not, are counseled on aspects of "positive living"[11] and are prescribed multivitamins.[12]

First-line drug regimens are prescribed by nurses and clinical officers according to standard protocols, and comprise lamivudine (3TC) plus nevirapine (NVP) plus either zidovudine (ZDV) or stavudine (d4T).[13] We start ZDV- or d4T-based regimens based mostly on drug availability but avoid ZDV in anemic patients (hemoglobin <10 g/dL). To avoid NVP-rifampin interactions, we defer ART for patients receiving acute-phase therapy for tuberculosis (TB) unless the CD4 cell count is less than 50/µL. In these instances, we start ART immediately with an efavirenz (EFV)–based regimen.[14,15] All patients starting ART are offered enrollment into a district wide program that uses community health workers for home-based, adherence monitoring (similar to regional models for directly observed TB therapy[16]). For those patients with CD4 cell counts less than 200/µL or in WHO stage IV, cotrimoxazole is administered. The initial follow-up schedule for those starting ART includes 6 visits during the first 3 months, with special focus on adherence and detecting adverse events. For individuals receiving a ZDV-containing regimen, hemoglobin levels are monitored closely, with scheduled checks at postinitiation weeks 2, 4, and 8.

Routine clinical follow-up for all patients occurs every 3 months, with CD4 cell counts performed every 6 months. Those patients receiving ART present monthly to the clinic to collect their antiretroviral drugs. Each dispensation includes a 2- to 3-day buffer of extra pills. We do allow preregistered family members or other treatment partners, also called "buddies," to collect a patient's medication. Adherence counseling is performed by nurses and pharmacy technicians. Patients who are receiving ART and who are more than 10 days late for a scheduled appointment are followed up in their homes by community health workers. Patients who are not receiving ART are not followed up until they are at least 30 days late. As the program expanded and our ability to track all patients was outstripped by the large enrollment numbers, we prioritized patients receiving ART for follow-up. Therefore, we were not able to attempt home visits for all late patients who were not yet receiving therapy.

Because routine use of viral load testing is not part of the Zambian national guidelines,[10] we rely on clinical estimates of treatment failure. *Treatment failure* is defined in our program and this analysis as (1) worsening WHO stage after at least 3 months of receiving therapy or (2) return of CD4 cell count to below pretreatment baseline. Some patients present with such profound immunosuppression and coexisting opportunistic illnesses that they die despite their ART completely suppressing the virus. We therefore evaluated treatment failure with and without death as a defining criterion in this analysis.

We also considered any patients who were switched to a second-line regimen, whether the above criteria were met or not, as having failed first-line therapy.

Laboratory Testing

A CD4 cell enumeration was performed at a central laboratory with a Beckman Coulter Epics XL-MCL 4-color Flow Cytometer (Beckman Coulter, Inc, Miami, Fla). Hemoglobin determinations were done centrally using the Sysmex XT2000i Analyzer[17] (Sysmex America, Inc, Mundelein, Ill). Some clinical facilities performed hemoglobin testing locally, using a field photometer assay (HemoCue AB, Helsingborg, Sweden).

Missed Visits and Patient Tracking

To track patient visits and allow monitoring of clinical quality and patient outcomes, we developed an electronic patient tracking system. At the end of each patient encounter, a data clerk enters key elements from the clinical forms into the patient tracking database.[8] The system tracks program performance indicators, tabulates pharmacy dispensation data, and generates lists of late patients needing follow-up. Late patients are sorted by their last CD4 cell count, so that priority can be given to tracking those who are most ill. Version 2.0 of the software, deployed February 1, 2005, captured a variety of additional information, including hemoglobin concentration and patient weight and height, which are important for the present analysis. Version 3.0 of the software, deployed October 10, 2005, had additional functionality, such as flagging patients with suspected treatment failure. Since the patient tracking system also serves as the clinic's appointment scheduler, these possible errors can often be noted and reviewed by a clinician prior to the patient's leaving the facility.

We assessed adherence to therapy in this analysis by timeliness of pharmacy attendance.[18-20] For each patient, we compared actual pharmacy visit dates with scheduled appointment dates and determined the cumulative number of days late a given patient was over the course of his or her time receiving ART. This variable was then standardized by dividing it by the total number of months a patient received therapy. Patients receiving ART who are more than 30 days late for a pharmacy appointment and who are not known to be dead or to have formally withdrawn from the program are considered late. Patient death is ascertained by reports from clinical facilities, home-based care organizations, and follow-up visits by community health workers. When available, the date of death is noted; when it is not, we assign the day of our last known encounter as the day of death.

Statistical and Analytic Methods

When assessing baseline characteristics among analysis groups, we compared continuous variables with an unpaired, 2-tailed *t* test and evaluated the normality assumption for each using the Kolmogorov-Smirnov test. We compared dichotomous and categorical variables with the Pearson χ^2 test statistic. We estimated hazard ratios (HRs) for time-to-event outcomes (eg, death or treatment failure) using Cox proportional hazards regression models,[21] and we tested the proportional hazards assumption for potential interaction between each variable and time in a given model using the likelihood ratio test. Variance inflation factor values indicated no colinearity among the predictors. The model assumptions thus being met, we report Cox HRs in this article. The adjusted models accounted for imperfect ascertainment of death increasing over time by including a term to adjust for calendar time at the initiation of therapy.

Individuals may often die outside the medical establishment, which is first indicated by a missed clinical or pharmacy visit. It may take some time for the follow-up teams to locate these individuals and ascertain their deaths. Thus, those individuals dying later in the analysis period would have had less opportunity to be ascertained as dead by the follow-up system than those dying earlier. Although the Cox model is valid regardless of the underlying hazard function as long as the proportional hazards assumption is met, any potential difference in ascertainment that occurs over time could change the underlying hazard function in a way that has nothing to do with the biology, which is the object of statistical inference. Thus, to control for this potential difference, a term for calendar time was included in the multivariate models that adjusts for the measurement error of the outcome in relation to the underlying hazard function. An objective of this approach was to provide a more precise estimate of the HRs. Reporting of results before and after 90 days was based on published convention.[22,23]

We fit Kaplan-Meier curves to examine survival functions stratified by CD4 cell count and WHO stage at initiation of therapy. In addition, we used the log-rank test to examine statistical difference among groups.

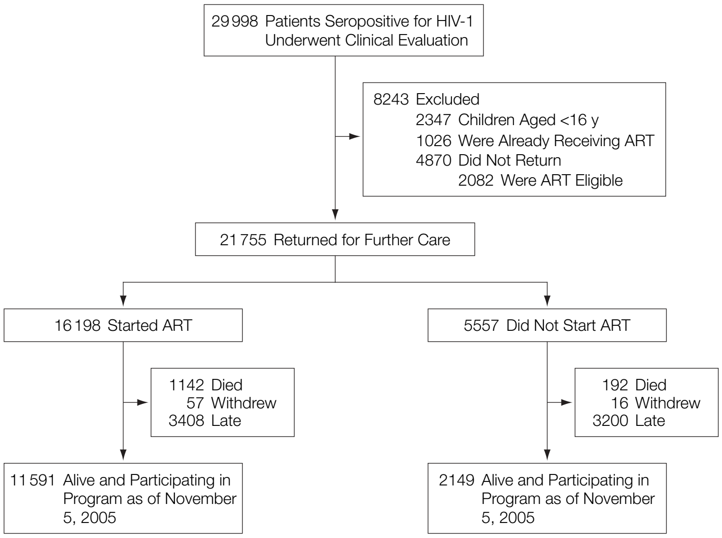
To evaluate factors associated with our definition of adherence to therapy, we used log-binomial regression to calculate the adjusted and unadjusted relative risk (RR) of being in the lower 25th and 10th percentile of adherence. Logistic regression is a commonly used method for estimating the RR via an odds ratio for binary outcomes in cohort studies (appropriate if the outcome is rare). If the outcome is not rare (>10%), however, the odds ratio generated with logistic regression will overestimate the RR. This problem was avoided in the analyses herein by generating the RR directly using log-binomial regression.[24,25]

Because our definition of adherence is based on pharmacy attendance, it is possible that sicker patients (those who have worse outcomes) might be less likely to come to the pharmacy, and thus be categorized as nonadherent. To mitigate this possible reverse causality effect, we performed a preplanned multivariable analysis where patients were categorized by their adherence behavior in the first 6 months of therapy, and only their 6- and 12-month outcomes were considered.

We estimated post hoc the smallest HRs that our available sample size and patient follow-up time could detect. We found that our cohort has 80% power (at $\alpha = .01$) to detect an HR for death of 1.26 among patients with active TB (assuming 11% of patients starting ART have active TB), and 80% power ($\alpha = .01$) to detect an HR for death of 1.17 among men (assuming 40% of patients starting therapy are male).

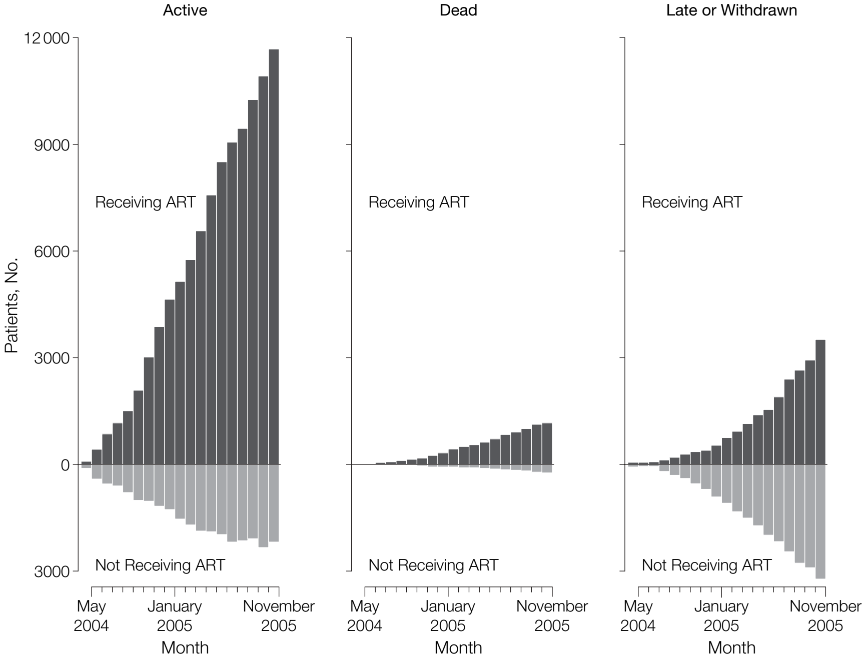
Our program measures repeat CD4 cell counts at 6-month intervals. Although this schedule is adequate for clinical management, it is not frequent enough to capture nonlinear CD4 cell

Figure 1. Description of an Antiretroviral Therapy Program Cohort, Lusaka, Zambia (April 2004-November 2005)


29 998 Patients Seropositive for HIV-1 Underwent Clinical Evaluation
8243 Excluded
2347 Children Aged <16 y
1026 Were Already Receiving ART
4870 Did Not Return
2082 Were ART Eligible
21 755 Returned for Further Care
16 198 Started ART
5557 Did Not Start ART
1142 Died
57 Withdrew
3408 Late
192 Died
16 Withdrew
3200 Late
11 591 Alive and Participating in Program as of November 5, 2005
2149 Alive and Participating in Program as of November 5, 2005

Profile of cohort of patients starting and not starting antiretroviral therapy. Patients starting antiretroviral therapy who are more than 30 days late for a scheduled pharmacy appointment and who are not known to be dead or to have formally withdrawn from the program are considered late. ART indicates antiretroviral therapy; HIV, human immunodeficiency virus.

Figure 2. Cumulative Status Over Time of Participants in the Antiretroviral Therapy Program, Lusaka, Zambia (April 2004-November 2005)



The number of participants in a given category (active, dead, late, or withdrawn) is presented at a given point in time. Of note, because of the dynamic nature of the cohort, individuals may be categorized as late 1 month but return for follow-up the next and be categorized as active. The status of each participant in the study is presented as of a particular moment in time, the end of each month. The first bar in each plot includes data from April 26 through May 1, 2004. The last bar in each plot includes data from October 2 through November 5, 2005. The other bars include data through the first of each month. The number of those not receiving antiretroviral therapy (ART) in the late or withdrawn category in November 2005 is 3216.

Table 1. Characteristics of the Entire Cohort at Entry of an Antiretroviral Therapy Program Cohort in Lusaka, Zambia (April 2004-November 2005)

	Entire Cohort				
	Not Starting ART		Starting ART		
	No.	Value	No.	Value	*P* Value
Age, median (range), y	5557	32 (16-79)	16 198	35 (16-89)	<.001*
Female, No. (%)	5557	3782 (68)	16 198	9864 (61)	<.001†
Weight, mean (SD), kg					
Female	2422	57.8 (22.0)	7245	52.8 (15.6)	<.001*
Male	1106	60.2 (10.2)	4522	56.5 (10.1)	<.001*
BMI, mean (SD)					
Female	2133	22.3 (4.3)	5861	20.6 (4.0)	<.001*
Male	1005	21.0 (3.4)	3647	19.7 (3.2)	<.001*
CD4 cell count, mean (SD) No. cells/µL	5370	352 (228)	15 336	143 (123)	<.001*
CD4 <50/µL, No. (%)		436 (8)		3283 (21)	<.001†
Hemoglobin, mean (SD), g/dL	2502	11.6 (2.3)	9271	10.7 (2.2)	<.001*
Hemoglobin <8 g/dL, No. (%)		173 (7)		954 (10)	<.001†
Tuberculosis (active), No. (%)	5557	283 (5)	16 198	1783 (11)	<.001†
WHO stage at entry, No. (%)	5445		15 866		
I		1939 (36)		1402 (9)	<.001†
II		1695 (31)		2891 (18)	
III		1645 (30)		9691 (61)	
IV		166 (3)		1882 (12)	

Abbreviations: ART, antiretroviral therapy; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; WHO, World Health Organization.
*Derived from the Student *t* test statistic.
†Derived from the Pearson χ^2 test statistic.

responses over time, particularly in those patients starting ART, where clinical trial data suggest an initial rapid increase in CD4 cell count, followed by a more modest rise.[26,27] For this reason, we elected to model CD4 cell responses over time for patients receiving and not receiving ART using the SAS MIXED Procedure (SAS Institute Inc, Cary, NC) with maximum likelihood estimation.

Fixed effects were included for time to repeat CD4 cell count from initiating therapy (for those receiving ART) or from enrollment (for those not receiving ART). Only those patients with at least 1 repeat measure were included, and a random intercept was included for each patient. Based on our anticipated nonlinear effects, we included polynomials for time to CD4 cell count as fixed effects and evaluated their contribution to the model based on the likelihood ratio test from the nested models. For patients not receiving ART, the quadratic term was significant (likelihood ratio, 5.7; $P=.02$). For patients receiving ART, the quadratic term was significant (likelihood ratio statistic=381.4; $P<.001$), as was the addition of the cubic term (likelihood ratio statistic=41.7; $P<.001$). We plotted the resulting predicted values of CD4 cell count over time from the fixed effects of the models.

A sensitivity analysis was performed that indicated that some predictors of failure or death also predicted loss to follow-up but with a much weaker association, and confirming our expectation that loss to follow-up likely represents a heterogeneous mixture of individuals, including some who have died (Stringer et al, unpublished data, May 2006).

All reported *P* values are 2-sided; we demanded significance at $P<.01$ to allow for multiple comparisons. This approach of requiring a more stringent *P* value is an accepted and conservative way of handling multiple comparisons, and the majority of the analyses herein were preplanned and informed by observations in other settings (eg, clinical trials); thus, the probability of rejecting the hypothesis of no association when no association in fact exists is very small.

The study data set was locked for analysis on November 5, 2005, and analysis was performed between that date and May 1, 2006, using SAS version 9.1.3 (SAS Institute, Inc). This analysis was deemed exempt[28] from human subjects review by the Institutional Review Boards of the University of Zambia, the US Centers for Disease Control and Prevention, and the University of Alabama at Birmingham.

RESULTS

Between April 26, 2004, and November 5, 2005, we evaluated 29 998 HIV 1 seropositive patients for entry into the Lusaka HIV Care and Treatment Program. Of these, 2347 (8%) were children (<16 years of age), and 1026 (3%) were receiving prior ART and are not considered further in this analysis. An additional 4870 (16%) did not return for a subsequent antiretroviral eligibility visit. Of those not returning, 2082 (44%) would have been eligible for ART.

Among the 21 755 HIV-infected treatment-naive adults who did return for an ART eligibility visit, 16 198 (74%) started ART and contributed a median of 207 days of follow-up to the analysis (interquartile range [IQR], 103-336 days), whereas 5557 patients (26%) did not start ART and contributed a median of 74 days to the analysis (IQR, 67-155 days). As of November 5, 2005, 11 591 patients (72%) who had started ART remained alive and active in the program, while 1142 (7%) had died, 57 (<1%) had withdrawn, and 3408 (21%) were late to follow-up (FIGURE 1 and FIGURE 2).

Baseline Characteristics

The 21 755 patients entering the program were a median of 35 years old (range, 16-89 years), and 13 646 (63%) were female. The mean (SD) entry body mass index (BMI, calculated as the weight in kilograms divided by the square of height in meters) of 7994 female patients and 4652 male patients with a baseline measure was 21.0 (4.2) and 19.9 (3.3), respectively. The mean (SD) CD4 cell count at entry among

20 706 patients with a baseline measurement was 197/μL (182/μL); 9363 patients (45%) had a CD4 cell count between 50/μL and 199/μL at entry, and 3719 patients (18%) had a CD4 cell count of less than 50/μL at entry. Of the 11 773 patients with a baseline hemoglobin, the mean (SD) concentration was 10.9 g/dL (2.2 g/dL), with 1127 patients (10%) having less than 8.0 g/dL.

Patients starting ART were older, less likely to be female, had lower mean BMI, and were more likely to have severe anemia compared with patients not initiating therapy (**Table 1** and **Table 2**). The mean (SD) CD4 cell count for those patients starting therapy was 143/μL (123/μL) compared with 352/μL (228/μL) among those not starting therapy. There were 11 573 of 15 866 patients (73%) starting ART with known initial WHO status who were in stage III or IV, compared with 1811 of 5445 patients (33%) not starting therapy.

Table 2. Characteristics of Those Starting or Not Starting an Antiretroviral Therapy Program at Entry in Lusaka, Zambia (April 2004-November 2005)

	Not Dead		Dead in 90 Days			Dead After 90 Days		
	No.	Value	No.	Value	*P* Value	No.	Value	*P* Value
Starting ART*								
Age, median (range), y	15 056	35 (16-89)	792	35 (16-83)	.85†	328	36 (16-68)	.04†
Female, No. (%)	15 056	9238 (61)	792	447 (56)	<.01‡	328	164 (50)	<.001‡
Weight, mean (SD), kg								
Female	6799	53.2 (15.8)	314	46.2 (9.1)	<.001†	120	49.7 (10.9)	<.001†
Male	4168	56.8 (10.1)	231	52.3 (9.9)	<.001†	118	55.2 (10.1)	.10†
BMI, mean (SD)								
Female	5477	20.7 (4.0)	269	18.3 (3.8)	<.001†	104	19.7 (4.1)	<.01†
Male	3338	19.8 (3.2)	197	18.0 (2.8)	<.001†	107	18.9 (3.2)	<.01†
CD4 cell count, mean (SD), No. cells/μL	14 251	146 (123)	756	99 (117)	<.001†	309	111 (97)	<.001†
CD4 <50/μL, No. (%)		2867 (20)		310 (41)	<.001‡		98 (32)	<.001‡
Hemoglobin, mean (SD), g/dL	8803	10.8 (2.2)	306	9.4 (2.2)	<.001‡	149	9.8 (2.1)	<.001†
Hemoglobin <8 g/dL, No. (%)		844 (10)	306	85 (28)	<.001‡	149	22 (15)	.03‡
Tuberculosis (active), No. (%)	15 056	1651 (11)	792	97 (12)	.26‡	328	35 (11)	.87‡
WHO stage at entry, No. (%)	14 747		773			324		
I		1367 (9)		21 (3)	<.001‡		14 (4)	<.001‡
II		2772 (19)		83 (11)			32 (10)	
III		8995 (61)		475 (61)			208 (64)	
IV		1613 (11)		194 (25)			70 (22)	
Not Starting ART§								
Age, median (range), y	5365	32 (16-79)	134	34 (17-61)	.10†	55	33 (20-72)	.64†
Female, No. (%)	5365	3673 (68)	134	72 (54)	<.001‡	55	35 (64)	.44‡
Weight, mean (SD), kg								
Female	2352	58.3 (22.1)	39	42.0 (10.8)	<.001†	29	45.6 (9.0)	<.001†
Male	1061	60.4 (10.3)	30	55.3 (8.2)	<.01†	15	53.3 (6.3)	<.001†
BMI, mean (SD)								
Female	2078	22.4 (4.3)	30	17.6 (3.5)	<.001†	25	18.5 (3.3)	<.001†
Male	965	21.0 (3.4)	26	19.6 (2.9)	.04†	14	18.4 (1.8)	<.001†
CD4 cell count, mean (SD), No. cells/μL	5193	359 (226)	121	103 (129)	<.001†	54	154 (157)	<.001†
CD4 <50/μL, No. (%)		359 (7)	121	58 (48)	<.001‡	54	19 (35)	<.001‡
Hemoglobin, mean (SD), g/dL	2423	11.6 (2.3)	50	9.1 (2.3)	<.001†	29	9.8 (2.6)	<.001†
Hemoglobin <8 g/dL, No. (%)		151 (6)	50	14 (28)	<.001‡	29	8 (28)	<.001‡
Tuberculosis (active), No. (%)	5365	254 (5)	134	21 (16)	<.001‡	55	7 (13)	<.01‡
WHO stage at entry, No. (%)	5263							
I		1931 (37)	129	3 (2)	<.001‡	51	5 (10)	<.001‡
II		1672 (32)	129	15 (12)		51	8 (16)	
III		1522 (29)	129	88 (68)		51	34 (67)	
IV		138 (3)	129	23 (18)		51	4 (8)	

Abbreviations: ART, antiretroviral therapy; BMI, body mass index, calulated as weight in kilograms divided by height in meters squared; WHO, World Health Organization.

*Twenty-two patients were excluded because of uncertain date of death.

†Derived from the *t* test statistic.

‡Derived from the Pearson χ^2 test statistic.

§Three patients were excluded because of uncertain date of death.

First-line Regimens

Among 16 198 patients starting ART, 6815 (42%) started a regimen of d4T + 3TC + NVP; 8094 (50%) started a regimen of ZDV + 3TC + NVP; 567 (3.5%) started ZDV + 3TC + EFV; 654 (4%) started d4T + 3TC + EFV; and 68 (0.5%) have missing data on initial antiretroviral regimen. Overall, 1601 patients (9.9%) were prescribed single-drug substitutions of their nucleoside reverse transcriptase inhibitor in response to drug intolerance or toxicity. Of 7469 patients, 442 (6%) switched from d4T to ZDV (switching rate, 13.0 per 100 patient-years; median time to switch, 108 days [IQR, 43-203]), whereas 1159 of 8661 patients (13%) switched from ZDV to d4T (switching rate, 27.1 per 100 patient-years; median time to switch, 84 days [IQR, 43-155]). Patients starting a ZDV-based regimen were considerably more likely over time to have that drug substituted compared with patients starting a d4T-based regimen (HR, 2.1; 95% CI, 1.9-2.4). There were 14 909 of 16 130 patients (92%) with initial drug information available who started a NVP-based regimen, and of these, 884 (6.0%) switched to EFV (switching rate, 12.0 per 100 patient-years; median time to switch, 74 days [IQR, 40-151]).

Survival

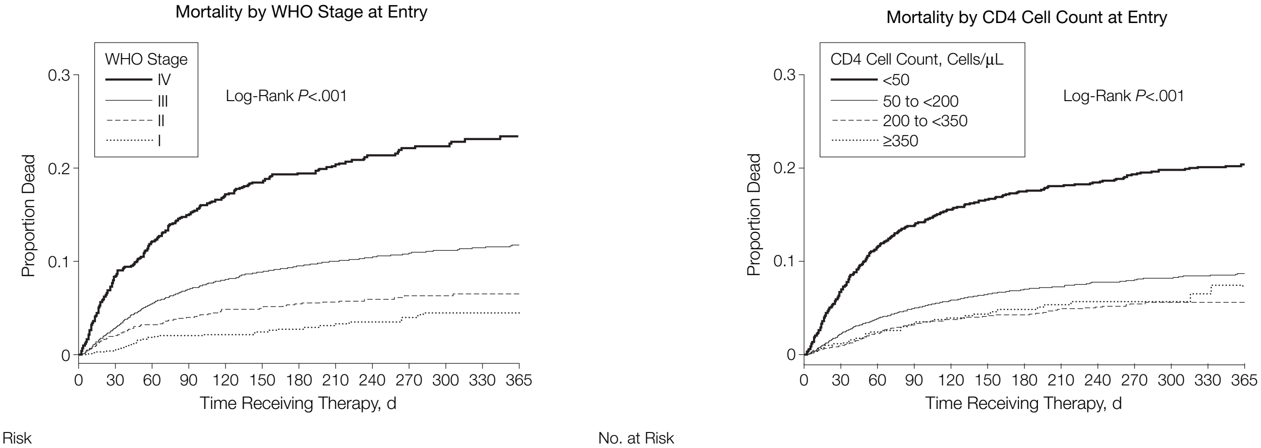
Of 12 369 patients at risk, 1120 died while receiving ART during 6977 patient-years of follow-up (this excludes late and withdrawn patients and those with uncertain date of death; mortality rate, 16.1 deaths per 100 patient-years; 95% CI, 15.1-17.0). In both crude and adjusted analyses, mortality was strongly associated with advanced WHO disease stage and low CD4 cell count at entry (Figure 3; Table 3).

Compared with those with a CD4 cell count of 200/µL or greater, patients with 50/µL to 199/µL and those with fewer than 50/µL were more likely to die (adjusted hazard ratio [AHR], 1.4; 95% CI, 1.0-2.0 and AHR, 2.2; 95% CI, 1.5-3.1, respectively). Compared with those patients entering care at WHO clinical stage I or II, patients entering at stage III and stage IV were more likely to die (AHR, 1.8; 95% CI, 1.3-2.4 and AHR, 2.9; 95% CI, 2.0-4.3, respectively). Initial CD4 cell count and WHO stage at entry represented independent and additive risks (Figure 4).

Other factors associated with death in multivariable analysis were BMI less than 16 (AHR, 2.4; 95% CI, 1.8-3.2), hemoglobin concentration less than 8.0 g/dL (AHR, 3.1; 95% CI, 2.3-4.0), and being among the 10% least adherent patients (AHR, 2.9; 95% CI, 2.2-3.9). Age and current therapy for TB were not associated with death (Table 3).

Of 1142 patients receiving ART who died, 1120 (98%) had a reliable date of death. Of these patients, 792 (71%) died within the first 90 days of commencing therapy (90-day mortality rate, 26 per 100 patient-years; 95% CI, 24-28), and an additional 328 (29%) died after 90 days of receiving therapy (post-90-day mortality rate, 5.0 per 100 patient-years; 95% CI, 4.5-5.6). Risk factors for death in the first 90 days were similar to those after 90 days (Table 4), except that the hazard associated with severe anemia was even greater (AHR, 3.6; 95% CI, 2.7-4.9). Risk factors for death after the first 90 days of receiving therapy also were similar to death overall, except that the effect of ane-

Figure 3. One-Year Mortality of Patients Starting Antiretroviral Therapy by Initial WHO Clinical Stage and CD4 Cell Count, Lusaka, Zambia (April 2004-November 2005)



No. at Risk

WHO Stage					
IV	1366	947	665	383	235
III	7361	5400	3947	2522	1423
II	2269	1604	1131	668	345
I	1137	841	606	366	222

No. at Risk

CD4 Cell Count, Cells/µL					
<50	2447	1588	1192	828	510
50 to <200	6631	4842	3480	2214	1257
200 to <350	2097	1627	1154	648	309
≥350	601	436	326	151	71

Kaplan-Meier curves were fit to examine survival functions stratified by CD4 cell count and WHO stage at initiation of therapy, and the log-rank test was used to examine statistical difference among groups. WHO indicates World Health Organization.

mia was attenuated and the effect of being male was more pronounced (AHR, 1.5; 95% CI, 1.0-2.3).

Regimen Failure

Of 11 714 patients at risk, 861 failed therapy by clinical criteria during 6568 patient-years of follow-up (this excludes late and withdrawn patients and those who died [crude failure rate, 13 failures per 100 patient-years; 95% CI, 12-14]). In multivariate analysis, patients with severe anemia at entry (AHR, 1.4; 95% CI, 1.0-1.9), males (AHR, 1.2; 95% CI, 1.0-1.5), and those with poor adherence (AHR, 1.8; 95% CI, 1.4-2.5) were more likely to experience regimen failure. Relative to those aged 41 years or older, patients aged 16 to 29 years were considerably less likely to experience treatment failure (AHR, 0.6; 95% CI, 0.5-0.8), whereas those in intermediate age categories had less dramatic but statistically significant protection against failure. Low CD4 cell count at entry also was protective against our clinical definition of failure. (It should be noted that since CD4 cell response is part of the failure definition, individuals with low baseline CD4 cell counts may be at artifactually lower risk of meeting this criterion since their CD4 cell counts are already low and simply cannot drop any further.) (Table 3).

CD4 Cell Count Response

The mean (SD) baseline CD4 cell count among patients starting ART was 143/μL (123/μL; data available from 15 336 of 16 198 patients [93%]). The mean (SD) increase in CD4 cell count among patients receiving treatment long enough to have a 6-month repeat measure was 155/μL (182/μL; data available from 4626 of 6253 patients [74%]). The mean (SD) increase in CD4 cell count in patients receiving treatment

Table 3. Factors Associated With Death, Treatment Failure, and Death or Treatment Failure Among Patients in an Antiretroviral Therapy Program Cohort in Lusaka, Zambia (April 2004-November 2005)

	Death				Treatment Failure*				Death or Treatment Failure			
	Crude			Adjusted (n = 5297)	Crude			Adjusted (n = 5043)	Crude			Adjusted (n = 5356)
	No.	Rate per 100 Patient-Years	HR (95% CI)†	HR (95% CI)†	No.	Rate per 100 Patient-Years	HR (95% CI)†	HR (95% CI)†	No.	Rate per 100 Patient-Years	HR (95% CI)†	HR (95% CI)†
WHO stage												
I and II	3546	8.2	1.0	1.0	3420	13.2	1.0	1.0	3568	20.9	1.0	1.0
III	7546	16.4	2.1 (1.7-2.5)	1.8 (1.3-2.4)	6934	12.7	0.9 (0.8-1.1)	1.0 (0.8-1.2)	7619	28.2	1.4 (1.2-1.5)	1.2 (1.0-1.4)
IV	1400	36.8	4.5 (3.7-5.5)	2.9 (2.0-4.3)	1141	12.3	0.9 (0.7-1.2)	1.1 (0.8-1.6)	1406	47.5	2.3 (2.0-2.6)	1.6 (1.3-2.1)
CD4 cell count, cells/ μL												
≥200	2797	9.4	1.0	1.0	2704	26.6	1.0	1.0	2842	35.1	1.0	1.0
≥50 to <200	6787	14.0	1.5 (1.3-1.9)	1.4 (1.0-2.0)	6321	11.1	0.4 (0.3-0.5)	0.4 (0.3-0.5)	6836	24.3	0.7 (0.6-0.8)	0.6 (0.5-0.7)
<50	2506	30.8	3.5 (2.9-4.2)	2.2 (1.5-3.1)	2103	3.6	0.1 (0.1-0.2)	0.1 (0.1-0.2)	2514	33.7	0.9 (0.8-1.1)	0.5 (0.4-0.6)
Tuberculosis												
Not active	11 399	16.4	1.0	1.0	10 496	12.6	1.0	1.0	11 487	28.1	1.0	1.0
Active	1334	17.0	1.1 (0.9-1.3)	1.0 (0.7-1.4)	1218	13.0	1.0 (0.8-1.3)	1.1 (0.8-1.4)	1348	29.1	1.1 (0.9-1.2)	1.0 (0.8-1.3)
BMI												
≥16	6959	12.0	1.0	1.0	6510	13.1	1.0	1.0	7033	24.4	1.0	1.0
<16	616	48.2	3.8 (3.1-4.5)	2.4 (1.8-3.2)	464	13.0	1.0 (0.7-1.4)	1.1 (0.7-1.6)	621	59.6	2.4 (2.0-2.8)	1.7 (1.4-2.2)
Hemoglobin, g/dL												
≥8	6823	8.5	1.0	1.0	6540	13.8	1.0	1.0	6887	21.7	1.0	1.0
<8	722	31.2	3.3 (2.7-4.1)	3.1 (2.3-4.0)	619	15.0	1.1 (0.9-1.5)	1.4 (1.0-1.9)	729	45.1	2.1 (1.7-2.4)	2.1 (1.8-2.6)
Sex												
Female	7855	14.4	1.0	1.0	7300	12.3	1.0	1.0	7915	26.0	1.0	1.0
Male	4878	19.8	1.4 (1.2-1.6)	1.2 (0.9-1.5)	4414	13.3	1.1 (1.0-1.3)	1.2 (1.0-1.5)	4920	31.9	1.3 (1.1-1.4)	1.2 (1.0-1.4)
Nonadherence												
<90th percentile	11 189	14.8	1.0	1.0	10 363	12.2	1.0	1.0	11 270	26.2	1.0	1.0
≥90th percentile	1073	34.4	2.3 (1.9-2.7)	2.9 (2.2-3.9)	913	18.5	1.6 (1.3-1.9)	1.8 (1.4-2.5)	1094	49.9	1.9 (1.7-2.2)	2.2 (1.8-2.7)
Age, y												
>41	3333	16.1	1.0	1.0	3058	13.9	1.0	1.0	3356	29.1	1.0	1.0
>35-≤41	2906	15.6	1.0 (0.8-1.2)	1.0 (0.7-1.3)	2684	13.0	0.9 (0.8-1.1)	0.8 (0.6-1.0)	2930	27.6	0.9 (0.8-1.1)	0.9 (0.7-1.0)
>30-≤35	3769	16.8	1.0 (0.9-1.2)	1.0 (0.8-1.4)	3463	11.8	0.8 (0.7-1.0)	0.7 (0.6-0.9)	3798	27.7	0.9 (0.8-1.0)	0.8 (0.7-1.0)
>15-≤29	2725	17.2	1.0 (0.9-1.2)	1.0 (0.7-1.4)	2509	12.0	0.9 (0.7-1.1)	0.6 (0.5-0.8)	2751	28.6	1.0 (0.8-1.1)	0.7 (0.6-0.9)
Time trend correction†				1.1 (1.0-1.1)				0.9 (0.9-1.0)				1.0 (1.0-1.0)

Abbreviations: BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; CI, confidence interval; HR, hazard ratio; WHO, World Health Organization.

*Treatment failure is defined in our analysis as (1) worsening WHO stage after at least 3 months of receiving therapy or (2) return of CD4 cell count to below pretreatment baseline. Category excludes patients who died but did not meet criteria for failure.

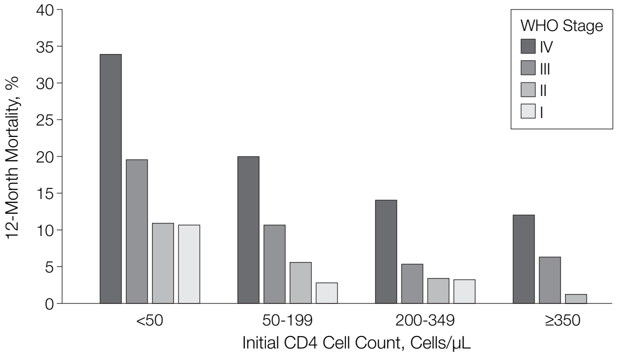
†Time since initiating therapy was included in the multivariate models to account for a number of possible cohort effects that are not likely to be related to the underlying biologically based hazard function. Among these are differences in ascertainment of death over time. Because many patient deaths are not detected until a scheduled visit has been missed and a follow-up team has been dispatched, those who died later in the analysis period would have had less opportunity to be discovered as dead than those who died earlier. Hazard ratios were estimated for the time-to-event outcomes of death, treatment failure, and death or treatment failure using Cox proportional hazards regression (SAS PHREG Procedure).

long enough to have a 12-month repeat measure was 175/μL (174/μL; data available from 1361 of 1784 patients [76%]). Patients not starting ART had a mean (SD) CD4 cell decline of 12/μL (215/μL; n=1096) at 6 months and 26/μL (217/μL; n=313) at 12 months (FIGURE 5).

Adherence to Therapy

The typical patient receiving therapy was 1.0 day late per month to pick up antiretroviral drugs from the clinic pharmacy. Of 16 198 patients receiving ART, 5215 (32%) were never late, whereas 1782 patients (11%) were late an average of 8.0 days or longer per month. Predictors of poor adherence by

Figure 4. One-Year Mortality Among Patients Starting Antiretroviral Therapy by Initial CD4 Cell Count and WHO Stage, Lusaka, Zambia (April 2004-November 2005)



Mortality is presented as a percentage within each stratum of WHO stage and CD4 cell count category at initiation of therapy. One-year mortality is reported because it is a standardized proportion (rather than a rate) that can be used to demonstrate the independent and additive effect of both WHO stage and CD4 cell count on survival. WHO indicates World Health Organization.

Table 4. Factors Associated With Early and Later Death Among Patients in an Antiretroviral Therapy Program Cohort in Lusaka, Zambia (April 2004-November 2005)*

	Death at or Before 90 Days				Death After 90 Days			
	Crude			Adjusted (n = 6041)	Crude			Adjusted (n = 4212)
	No.	Rate per 100 Patient-Years	HR (95% CI)	HR (95% CI)	No.	Rate per 100 Patient-Years	HR (95% CI)	HR (95% CI)
WHO stage								
I and II	3817	12.7	1.0	1.0	2430	0.7	1.0	1.0
III	8606	25.3	2.0 (1.6-2.5)	1.7 (1.1-2.5)	5374	1.4	2.0 (1.4-2.7)	2.0 (1.1-3.4)
IV	1604	57.2	4.5 (3.6-5.7)	2.8 (1.7-4.5)	941	2.8	3.9 (2.7-5.7)	3.4 (1.8-6.8)
CD4 cell count, cells/μL								
≥200	3120	13.6	1.0	1.0	2055	0.9	1.0	1.0
≥50 to <200	7632	21.3	1.6 (1.2-2.0)	1.4 (1.0-2.2)	4819	1.3	1.5 (1.1-2.1)	1.4 (0.8-2.4)
<50	2868	52.6	3.8 (3.1-4.8)	2.3 (1.5-3.5)	1576	2.1	2.5 (1.8-3.6)	1.8 (1.0-3.2)
Tuberculosis								
Not active	12 744	25.3	1.0	1.0	7945	1.4	1.0	1.0
Active	1562	28.1	1.1 (0.9-1.4)	1.2 (0.8-1.7)	948	1.3	1.0 (0.7-1.4)	0.7 (0.4-1.3)
BMI								
≥16	7775	20.0	1.0	1.0	5234	1.1	1.0	1.0
<16	694	83.1	4.1 (3.3-5.1)	2.4 (1.7-3.4)	389	3.0	2.7 (1.9-3.9)	2.2 (1.3-3.7)
Hemoglobin, g/dL								
≥8	7548	13.0	1.0	1.0	5295	0.9	1.0	1.0
<8	827	48.3	3.7 (2.9-4.7)	3.6 (2.7-4.9)	478	1.8	2.1 (1.4-3.4)	1.5 (0.8-2.8)
Sex								
Female	8729	23.6	1.0	1.0	5532	1.1	1.0	1.0
Male	5577	28.8	1.2 (1.1-1.4)	0.9 (0.7-1.3)	3361	1.8	1.7 (1.4-2.1)	1.5 (1.0-2.3)
Nonadherence								
<90th percentile	12 469	23.8	1.0	1.0	7932	1.2	1.0	1.0
≥90th percentile	1333	43.1	1.8 (1.5-2.2)	2.3 (1.6-3.2)	669	3.2	2.7 (2.0-3.6)	2.9 (1.7-5.0)
Age, y								
>41	3715	24.5	1.0	1.0	2411	1.6	1.0	1.0
>35 to ≤41	3243	25.0	1.0 (0.8-1.3)	1.0 (0.7-1.5)	2044	1.4	0.9 (0.6-1.2)	0.9 (0.5-1.6)
>30 to ≤35	4217	27.2	1.1 (0.9-1.3)	1.1 (0.8-1.6)	2620	1.2	0.8 (0.6-1.0)	0.9 (0.5-1.4)
>15 to ≤29	3131	25.6	1.0 (0.9-1.3)	0.9 (0.6-1.3)	1818	1.4	0.9 (0.7-1.3)	1.1 (0.7-2.0)
Time trend correction*				1.1 (1.0-1.1)				1.0 (1.0-1.1)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CI, confidence interval; HR, hazard ratio; WHO, World Health Organization.

*See caption of Table 3 for explanation. Hazard ratios were estimated for the time-to-event outcomes of death, before and after 90 days, using Cox proportional hazards regression (SAS PHREG Procedure).

our definition of being among the 10% least adherent patients included hemoglobin concentration less than 8.0 g/dL (RR, 1.4; 95% CI, 1.1-1.8), WHO stage III disease (RR, 1.3; 95% CI, 1.1-1.6), and WHO stage IV disease (RR, 1.6; 95% CI, 1.2-2.1). Patient age, sex, CD4 cell count at entry, TB coinfection, and BMI did not predict poor adherence.

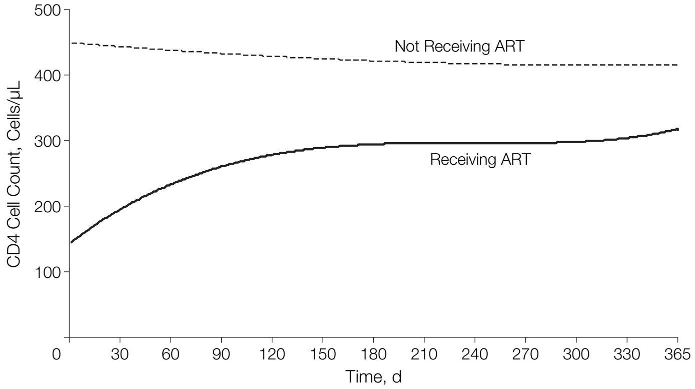
Nonadherent patients had worse CD4 cell responses at 12 months than adherent patients. Patients at or below the 25th percentile for adherence had a mean CD4 cell increase of 29/μL less than those above the 25th percentile (156/μL vs 185/μL; $P = .004$; n=437 and 922, respectively), whereas patients at or below the 10th percentile for adherence had a median CD4 cell increase of 51/μL less than those above the 10th percentile (129/μL vs 180/μL; $P = .003$; n=112 and 1247, respectively).

In multivariable analyses in which patients were categorized by their adherence behavior in the first 6 months of therapy and their 6- and 12-month outcomes were analyzed controlling for WHO stage at entry, BMI, and entry hemoglobin values, we found a strong association between poor adherence (10% least adherent) and both death (AHR, 5.5; 95% CI, 2.1-13.9; n for model=3810) and treatment failure (AHR, 1.8; 95% CI, 1.3-2.5; n for model=3825).

COMMENT

Our experience in Zambia indicates that massive, rapid scale-up of AIDS treatment services is feasible in urban sub-Saharan Africa and that favorable clinical outcomes are possible in settings where nurses and clinical officers provide the majority of the care. Most mortality for patients starting ART occurs early and among those with very advanced HIV disease at presentation. Among the surviving majority, the CD4 cell response is generally vigorous for those starting ART. Although our experience is still early, we have observed that the WHO recommended first-line regimens are fairly well tolerated and associated with adherence rates comparable with those in the United States.[20]

Figure 5. Modeled Changes in CD4 Cell Count Over Time for Surviving Patients Who Received or Did Not Receive Antiretroviral Therapy, Lusaka, Zambia (April 2004-November 2005)



CD4 cell count trajectories were estimated from mixed modeling using maximum likelihood estimation and a random effect for individual (see METHODS). Only those patients with repeat measures were included in the modeled estimates. ART indicates antiretroviral therapy.

The Lusaka program is perhaps the largest single cohort of patients receiving ART yet to be described. As of April 30, 2006, a total of 39 872 patients had been enrolled into HIV care and treatment, and 25 542 started ART. The rapid expansion of the program and its favorable clinical outcomes can, we believe, be attributed to 4 major factors: First, the Zambian government has provided key leadership and political advocacy for the program's success, typified by its decision to eliminate district medical fees for all patients seeking HIV care and treatment. This decision has helped ensure equal access for women, children, and other disadvantaged groups.

Second, the use of clinical officers and nurses to provide care according to standard care protocols allowed the program to circumvent the critical physician shortage currently faced by the country. A typical clinic with a dozen clinical officers and nurses may share a single physician with a nearby facility.

Third, our electronic patient tracking and outcomes monitoring system, which was recently adopted as the national standard for Zambia, has been critical for effective scale-up. Through capture of individual-level patient data in real time, the system is able to generate facility-level reports that aid in both clinic management and patient care. The system allows for collection and analysis of aggregate outcomes data (as we report herein), encourages compliance with treatment protocols, tracks pharmaceutical usage, and generates lists of patients needing home follow-up.

And fourth, the huge financial resources made available by PEPFAR should be acknowledged. This funding has allowed the rapid implementation and maintenance of a complex and resource-intensive care system that has saved many lives. This effort simply would not have been possible without the Emergency Plan.

Like other published reports,[22,23,29,30] we found that the majority of patient deaths in our setting occur within the first 3 months of ART initiation. This result indicates that particular attention should be paid to patients as they start ART, particularly those with advanced disease, and it raises the possibility that some early mortality may be attributable to undiagnosed opportunistic infections, nutritional deficiencies,[31] endocrine abnormalities such as hypoadrenalism,[32] or severe immune reconstitution inflammatory syndrome,[33] although we have no direct evidence to support these proposed causes.

One obvious way to reduce early mortality would be to identify patients earlier in the course of disease and start ART before they become wasted and anemic.[13] Currently, a major barrier to getting patients into care early is stigma; people tend not to seek diagnosis until they are quite ill. However, it is hoped that widespread availability of effective ART in Zambia will reduce AIDS stigma and encourage people to seek diagnosis and medical attention earlier, as has been observed in the United States and other developed countries.[34]

Our program's mortality rate after the first 90 days (5.0 deaths per 100 patient-years), is comparable with that observed in developed world settings. As an example, the post-90-day mortality rate among patients starting therapy at the University of Alabama at Birmingham's outpatient AIDS clinic is 4.34 per 100 patient-years (M. Saag et al, unpublished data, April 2006). Similarly, the CD4 cell responses observed in our cohort is comparable with that observed in developed world settings.[35-37] These data provide additional evidence that treatment outcomes in very large, government-owned programs in Africa may match those in the developed world.

Unlike other reports,[38-40] we did not find a significant association between TB coinfection and death, even during the first 90 days when mortality is highest. This finding can be partially explained by limitation in our ascertainment of new TB infections. New TB infections occurring while patients are receiving ART are not well diagnosed in our setting, although the Lusaka District hopes to soon improve diagnosis of these new infections through the introduction of targeted TB culture. In addition, the majority of patients identified with active TB are referred from specialty TB departments within each facility. Since many patients have been taking anti-TB therapy for weeks to months, the survival differences between those infected and those not infected are likely attenuated.

The principal limitation of our analysis is the relatively high number of late and lost-to-follow up patients. This issue is particularly significant among those patients not yet starting ART, whose high rate of loss to-follow-up could bias certain outcomes, such as CD4 cell response. Although this program is not a clinical trial or formal research cohort, we generally make at least one attempt to bring late patients back into care via a home follow-up visit. A recent review of these follow-up activities at 11 ART sites in Lusaka revealed that of 1366 late patients for whom home follow-up visits were made, 565 (41%) were untraceable because they had given an invalid address or had moved, 366 (27%) were dead, and 435 (32%) were located and reminded to return to the clinic. Of those reminded, 122 (28%) actually returned, compared with 68 of 565 (12%) of untraceable patients who returned (Krebs et al, unpublished data, June 2006). These data suggest that up to 19 home-visit attempts must be made to generate a single return visit among those classified as late. Similar experiences have been reported elsewhere in the region.[41] Thus, while the home follow-up visit has been useful for ascertaining death outcomes, it has proven inefficient and relatively expensive for generating return patient visits.

CONCLUSIONS

In summary, with the support of PEPFAR and other funding agencies, the Zambian Ministry of Health has demonstrated that roll out of HIV care and treatment services in urban primary care sites is feasible on a large scale while maintaining favorable patient outcomes. Yet, many challenges remain. There continues to be tremendous pressure, and indeed, an ethical mandate, to continue scaling-up of services across the country, particularly in remote regions where people have difficulty accessing care. Meanwhile, the more established Lusaka ART sites have begun to struggle with operational issues, such as patient overload and staff burnout, as well as difficult longer-term AIDS clinical management issues, such as multiple regimen failure, long-term adverse effects, and program attrition.

Despite the burgeoning availability of ART, HIV prevention remains critical in Zambia, where each year an estimated 100 000 adults and children become infected and an additional 100 000 already infected individuals meet criteria for ART initiation. We believe the early success of the Lusaka District ART Program calls for optimism. This experience demonstrates that it is possible, given proper resources and local government commitment, to treat many thousands of people in urban African settings.

Author Contributions: Dr Stringer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: J. Stringer, Zulu, Levy, E. Stringer, Mwango, Chi, Mtonga, Cantrell, Bulterys, Saag, Mwinga, Sinkala.
Acquisition of data: J. Stringer, Levy, Reid.
Analysis and interpretation of data: J. Stringer, Zulu, Levy, E. Stringer, Mwango, Chi, Mtonga, Cantrell, Bulterys, Saag, Marlink, Ellerbrock, Sinkala.
Drafting of the manuscript: J. Stringer, Levy, Bulterys, Saag.
Critical revision of the manuscript for important intellectual content: J. Stringer, Zulu, Levy, E. Stringer, Mwango, Chi, Mtonga, Reid, Cantrell, Bulterys, Saag, Marlink, Mwinga, Ellerbrock, Sinkala.
Statistical analysis: J. Stringer, Levy, Cantrell.
Obtained funding: J. Stringer, Bulterys, Marlink, Mwinga.
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Study supervision: J. Stringer, Zulu, Levy, E. Stringer, Mwango, Chi, Mtonga, Reid, Cantrell, Bulterys, Sinkala.

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