

Outcomes of Antiretroviral Treatment Programs in Rural Southern Africa

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Background: Data on outcomes of antiretroviral treatment (ART) programs in rural sub-Saharan African are scarce. We describe early losses and long-term outcomes in 6 rural programs in Southern Africa with limited access to viral load monitoring and second-line ART.

Methods: Patients aged ≥ 16 years starting ART in 2 programs each in Zimbabwe, Mozambique, and Lesotho were included. We evaluated risk factors for no follow-up after starting ART and mortality and loss to follow-up (LTFU) over 3 years of ART, using logistic regression and competing risk models. Odds ratios and sub-distribution hazard ratios, adjusted for gender, age category, CD4 category, and World Health Organization stage at start of ART are reported.

Results: Among 7725 patients, 449 (5.8%) did not return after initiation of ART. During 9575 person-years, 698 (9.6%) of those with at least 1 follow-up visit died, and 1319 (18.1%) were LTFU. At 3 years, the cumulative incidence of death and LTFU were 12.5% (11.5%–13.5%) and 25.4% (24.0%–26.9%), respectively, with important differences between countries as follows: in Zimbabwe 75.1% (72.8%–77.3%) were alive and on ART at 3 years compared with 55.4% (52.8%–58.0%) in Lesotho and 51.6% (48.0%–55.2%) in Mozambique. In all settings, young age and male gender predicted

LTFU, whereas advanced clinical stage and low baseline CD4 counts predicted death.

Conclusions: In African ART programs with limited access to second-line treatment, mortality, and LTFU are high in the first 3 years of ART. Low retention in care is a major threat to the sustainability of ART delivery in Southern Africa, particularly in rural sites.

Key Words: antiretroviral treatment, cohort study, retention in care, rural Southern Africa

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INTRODUCTION

The World Health Organization (WHO) estimates that more than 5 million HIV-1-infected people were receiving antiretroviral therapy (ART) in low-income and middle-income countries by the end of 2009.¹ However, high mortality and loss of patients to follow-up in the context of the rapid scale-up of ART and weak health systems challenge clinical and programmatic outcomes in low-income settings in Africa.^{2,3} In recent years, an increasing body of evidence, including 2 systematic reviews, has shown low retention in care of patients starting ART in sub-Saharan Africa.^{4–7} Early losses after the initiation of ART have been recognized as important barriers to the success of ART programs in resource-constrained settings.^{8,9} According to a recent report based on aggregate data from national programs, retention in care in countries in sub-Saharan Africa is estimated to be as low as 75.2% at 12 months, possibly due to high early mortality.¹⁰

Data on short-term and long-term clinical and programmatic outcomes in rural sub-Saharan Africa, especially in settings with limited diagnostic possibilities, access to viral load testing and second-line ART, are scarce. Due to many structural factors influencing the scale-up of ART, the distribution of services may be inequitable between rural and urban African settings.¹¹ For instance, the impact of the chronic shortage of health care workers has been most devastating in rural settings.¹²

Mozambique, Zimbabwe, and Lesotho are 3 countries with a high prevalence of HIV infection where ART delivery has been scaled up in the last few years. Despite the substantial increase in patients starting ART, only 30%, 34%, and 48% of

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the HIV-infected population in need of treatment in Mozambique, Zimbabwe, and Lesotho, respectively, were estimated to have access to ART by 2009.¹ In this context, SolidarMed, a Swiss nongovernmental organization, established the SolidarMed AntiRetroviral Treatment (SMART) program in 2005,¹³ with a focus on supporting the delivery of ART and health care in rural settings in sub-Saharan Africa. We examined the importance of no follow-up after initiation of ART and mortality and loss to follow-up (LTFU) over 3 years of ART in the SMART programs in Zimbabwe, Mozambique, as well as Lesotho.

METHODS

SMART Program

The SMART program was launched in rural Zimbabwe, Mozambique, and Lesotho in 2005 to support the national ART programs by introducing voluntary testing and counseling services, antiretroviral drugs for the prevention of mother-to-child transmission of HIV, and by providing ART and treatments of opportunistic diseases. Although national authorities and health systems continued to manage services, SolidarMed facilitated implementation, bridged gaps in funding, and supported capacity building and monitoring. Subsequently, the program was expanded to 9 district health facilities and more than 40 affiliated peripheral health centers in Lesotho (3 districts), Zimbabwe (2 districts), Mozambique (2 districts), and Tanzania (2 districts).

All ART programs included in this study are rural. Sixty percent of patients in Lesotho and 90% of those in Mozambique and Zimbabwe were subsistence farmers and most of them were illiterate. Every ART program has a well-defined catchment area, which includes between 55,000 people in Lesotho and 240,000 in Mozambique. Programs are nurse led, with only 2 medical doctors in Mozambique, 4 in Lesotho, and 5 in Zimbabwe, and there is usually only 1 functioning ambulance per area. Finally, most patients travel between 1 and 3 hours to the clinic, and distances to the next referral clinic can be up to 240 kilometers, depending on the area.

The programs in Zimbabwe and Mozambique are part of the International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA), a collaboration of ART programs from 7 countries in the region. The IeDEA networks in sub-Saharan Africa have been described in detail elsewhere.¹⁴ In the present study, we analyzed data from the SMART programs in Zimbabwe, Mozambique, and Lesotho.

Data Collection

SolidarMed supports the monitoring of ART programs through the provision and maintenance of a purpose-built clinical database. Data entry clerks are trained by senior local data managers. Data are prospectively recorded on standardized national patient forms by clinical nurses and entered by data clerks into the database, which is the same at all sites. Data collection starts on the day ART is initiated and continues at each visit to the clinic. Information on demographic characteristics such as date of birth, marital status, occupation, residency, and past medical history, including year of diagnosis

of HIV infection and prior CD4 counts is recorded on the first day. Clinical parameters, including height, weight, opportunistic infections, and WHO stage and laboratory parameters are recorded at baseline and during follow-up. Treatment adherence is monitored by 2 means as follows: pill counts and adherence to medical appointments.

Local data supervisors regularly perform random quality checks on site, comparing entered data with paper forms. Twice a year, an additional quality check is performed with the help of staff at SolidarMed head quarters in Lucerne, Switzerland, and the Institute of Social and Preventive Medicine at the University of Bern, Switzerland. Personal identifiers are removed before transfer of the data for statistical analysis. The present analysis includes all data available up to the end of June 2010.

Counseling, Follow-up, and Tracing of Patients

Three individual or group adherence counseling sessions are normally held before the initiation of ART, and further adherence counseling takes place during ART, if required. Most patients are seen by nurses, and follow-up visits are scheduled according to national algorithms, generally every month. All new clinical events, such as pregnancy and opportunistic infections, are recorded whenever patients seek medical care. CD4 counts are determined every 3–6 months, depending on the clinic. Further laboratory examinations include hemoglobin, total white cell count, total lymphocyte count, platelets, alanine transaminase, and creatinine (only in Lesotho). All changes to the antiretroviral treatment regimens, serious adverse effects, and the prescription of prophylactic treatments are recorded. There are no death registries in Lesotho and Mozambique, and ascertainment of deaths occurring outside health facilities, therefore, relies on reports from outreach workers or direct information by families, friends, or local authorities. Whenever patients have missed their last appointment at the treatment site, they are traced through home visits by nurses, volunteers, lay counselors, or community associations.

Inclusion Criteria and Outcomes

All patients aged 16 years or older with complete data on sex and date of birth who started ART consisting of at least 3 drugs between January 2005 and June 2010 were included in the analysis. We examined 3 outcomes as follows: no follow-up after starting ART, LTFU, and death. LTFU was defined as not returning to the facility for 6 months or longer. Patients who started ART within the last 6 months before the closing date of this analysis were therefore excluded from this study. Follow-up of patients transferred to another clinic was censored at the date of their last visit. Retention in care was defined as alive on ART and in active follow-up over the study period.

Statistical Analyses

We identified risk factors for no follow-up after starting ART using logistic regression. Variables at the start of ART

included in the model were sex, age (16–29, 30–39, 40 years and older), CD4 cell count (0–49, 50–99, 100–199, 200 cells/ μ L and over), WHO stage (I/II or III/IV), calendar year (before 2008, 2008, and after 2008), country, and initial treatment regimen (nevirapine based or efavirenz based).

We used logistic regression to identify factors associated with not returning to the clinic after initiation of ART and competing risk models to analyze mortality and LTFU. Death is a competing risk of LTFU: patients who die can no longer become lost to follow-up. Similarly, deaths in patients who are lost to follow-up are no longer recorded in the database. Standard time-to-event analyses, for example Kaplan–Meier curves, ignore the competing risks of death and LTFU and may produce biased results. We therefore plotted stacked competing risk cumulative incidence curves of LTFU and mortality up to 3 years after starting ART.¹⁵ Furthermore, we used the competing risk subdistribution models described by Fine and Gray¹⁶ to examine risk factors for LTFU or death. All statistical analyses were performed using Stata (version 11, Stata Corporation, College Station, TX).

Ethical Approval

We obtained ethical approval for the collection and transfer of data from the Comité Nacional de Bioética para a Saude, Republica de Moçambique, the Medical Research Council of Zimbabwe and the Ministry of Health and Social Welfare of Lesotho for the SMART programs in Mozambique, Zimbabwe, and Lesotho, respectively. In the case of Lesotho, the ethical clearance was issued to SolidarMed and its main partner, the Christian Health Association of Lesotho. In Mozambique, the ethics committee required individual informed consent, whereas informed consent was not required in Zimbabwe or Lesotho.

RESULTS

Characteristics of Clinics and Patients

The 6 ART programs differed in terms of the number of nurses, medical officers, and doctors seeing patients, travel times of patients, and first-line regimens used (Table 1). Staffing was lowest in Mozambique, where only around 20 nurses and 1 or 2 medical doctors were available per 100,000 population. The mean travel time to the clinic ranged from 1 hour in Zaka, Zimbabwe, to 3 hours in Ancuabe, Mozambique. All sites except Ancuabe had flow cytometry to count CD4 cells on site, but no facility had direct access to viral load monitoring. A fixed-dose combination of stavudine, lamivudine, and nevirapine was the most prescribed ART regimen during the study period. In Lesotho, zidovudine, or tenofovir were used increasingly in first-line ART in recent years. More than 90% of patients were treated with a nevirapine-based regimen, and only 3 different ART regimens were used to treat more than 95% of patients in Mozambique and Zimbabwe. In Lesotho, more than half of patients received an efavirenz-based initial regimen, and the number of treatment options was higher due to the increasing availability of tenofovir.

During the study period, protease inhibitors were not available or not used depending on the site.

A total of 9271 patients started ART during the study period. We excluded patients with incomplete data on sex or age ($n = 26$) and patients who started ART less than 6 months before the closing date of the database ($n = 1520$): 7725 patients were therefore included in analyses. In all clinics, the majority of patients were women; overall 5018 (65%) were female (Table 2). Patients in Mozambique were younger than those starting ART in the 2 other countries. Median CD4 cell counts at start of ART ranged from 91 cells per microliter in Zaka, Zimbabwe, to 279 cells per microliter in Ancuabe, Mozambique. The proportion of patients in advanced clinical stage (WHO stage III/IV) was high in all clinics ranging from 48.3% in Seboche, Lesotho, to 94.8% in Chiure, Mozambique.

Patients With No Follow-Up After Starting ART

Overall, 449 patients (5.8%) were not seen after the ART initiation visit, with large variations between countries (Table 1). In Mozambique, 21.8% of patients who started ART in Ancuabe and 8.9% of patients from Chiure did not return, whereas in Zimbabwe and Lesotho, the proportion of patients with no follow-up was below 5%. Younger age and, to a lesser extent, male gender were associated with the probability of no follow-up (Table 3). Patients with CD4 cell counts below 50 cells per microliter or missing CD4 counts at baseline were also more likely not to return to the health facility after the start of ART. The risk of no follow-up was higher in Mozambique than in the 2 other countries. Finally, the probability of not returning after the first visit was higher in more recent years (Table 3).

Mortality and LTFU

During 9575 person-years of follow-up, 1319 patients (18.1%) of the 7276 patients with at least 1 follow-up visit were LTFU, and 698 patients (9.6%) died. The crude mortality rate was 7.3 (95% confidence interval: 6.8 to 7.9) deaths per 100 person-years and the rate of LTFU 13.8 (13.1 to 14.5) per 100 person-years. There were important differences between countries as follows: Figure 1 shows cumulative percentages from competing risk models of patients alive and on ART, patients lost to follow up, and deaths for Zimbabwe, Lesotho, and Mozambique. At 3 years, 9.0% (95% confidence interval: 7.6 to 10.5) were known to have died in Zimbabwe, 15.7% (13.9 to 17.6) were lost to follow-up, and 75.1% (72.8 to 77.3) were alive and on ART. The figures were less favorable for Mozambique as follows: 17.4% (14.9 to 20.0); 31.0% (27.8 to 34.2); and 51.6% (48.0 to 55.2), respectively, with Lesotho in an intermediate position (Fig. 1).

Male gender, advanced clinical stage, and CD4 cell counts below 50 cells per microliter at ART initiation were consistently associated with higher mortality (Table 3). Older patients and females were less likely to be LTFU over the

TABLE 1. Characteristics Of the Six Antiretroviral Therapy Programmes Included in the Analyses

	Zimbabwe		Mozambique		Lesotho	
	Bikita	Zaka	Chiure	Ancuabe	Seboche	Paray
Number of patients	1777	1254	843	574	1427	1850
Start of program	2006	2005	2005	2008	2005	2005
Population covered	165,000	193,000	250,000	125,000	55,000	77,000
Medical doctors per 10,000 population	0.2	0.3	0.1	0.2	0.7	0.5
Other health workers per 10,000 population*	10.3	11.3	1.6	2.4	12.2	10.0
Mean travel time to clinic (hrs)	2	1	2	3	1.5	2
Patients with travel time over 2 hours (%)	40	20	35	50	35	45
CD4 count on site	Yes†	Yes†	Yes†	No	Yes†	Yes†
Three most common ART regimens prescribed‡	3TC/D4T/ NVP (91%) 3TC/D4T/ EFV (5%) 3TC/ZDV/ NVP (4%)	3TC/D4T/ NVP (85%) 3TC/ZDV/ NVP (7%) 3TC/D4T/ EFV (6%)	3TC/D4T/ NVP (87%) 3TC/ZDV/ NVP (6%) 3TC/D4T/ EFV (6%)	3TC/D4T/ NVP (80%) 3TC/ZDV/ NVP (11%) 3TC/D4T/ EFV (9%)	3TC/TDF/ EFV (28%) 3TC/ZDV/ NVP (25%) 3TC/ZDV/ EFV (23%)	3TC/D4T/ NVP (42%) 3TC/TDF/ EFV (17%) TC/ZDV/ NVP (15%)
Number of ART regimens to treat 95% of patients	2	3	3	3	6	5
Number of patients with no follow-up	76 (4.3%)	53 (4.2%)	75 (8.9%)	125 (21.8%)	32 (2.2%)	88 (4.8%)

*Other health workers related to nurses, medical officers, pharmacists, and laboratory technicians.

†Available in main hospitals but not in peripheral health centers.

‡ART regimens prescribed are 3TC, lamivudine; D4T, stavudine; EFV, efavirenz; NVP, nevirapine; TDF, tenofovir; ZDV, zidovudine.

3 years after starting ART, whereas the risk of LTFU was highest in patients without a CD4 cell count at the start of ART and if treatment was initiated after 2007, compared with the other groups. Patients in Zimbabwe were less likely to be lost to follow-up than those treated in Lesotho or Mozambique.

DISCUSSION

In this study of 6 ART programs in rural Mozambique, Zimbabwe, and Lesotho, we found that the proportion of patients with no follow-up after starting ART differed from one setting to the other, reaching more than 20% in the most remote setting in Mozambique. Retention in care over the first

TABLE 2. Sociodemographic and Clinical Characteristics of Patients at the Start of Antiretroviral Therapy

	Zimbabwe		Mozambique		Lesotho		Total
	Bikita	Zaka	Chiure	Ancuabe	Seboche	Paray	
Number of patients	1777	1254	843	574	1427	1850	7725
Number of women (%)	1232 (69.3)	820 (65.4)	480 (56.9)	349 (60.8)	975 (68.3)	1162 (62.8)	5018 (65.0)
Median age in years (IQR)	39 (34–47)	39 (34–47)	33 (27–41)	31 (25–38)	39 (34–47)	38 (31–47)	38 (32–46)
Median absolute CD4 count/ μ L (IQR)	121 (61–182)	91 (46–147)	201 (112–314)	279 (156–418)	163 (91–269)	170 (88–262)	153 (77–248)
Missing (%)	512 (28.8)	653 (52.1)	138 (16.3)	176 (30.7)	83 (5.8)	180 (9.7)	1742 (22.6)
WHO stage (%)							
I/II	321 (18.1)	153 (12.2)	44 (5.2)	84 (14.6)	738 (51.7)	947 (51.1)	2,287 (29.6)
III/IV	1456 (81.9)	1101 (87.8)	799 (94.8)	490 (85.4)	689 (48.3)	903 (48.8)	5438 (70.4)
Median weight in kg (IQR)	54 (48–60)	55 (48–62)	46 (40–52)	47 (42–54)	55 (49–62)	55 (49–62)	53 (46–60)
Missing (%)	19 (1.0)	36 (2.8)	40 (4.7)	5 (0.9)	4 (0.3)	108 (5.8)	212 (2.7)
Type of first-line ART							
NVP based (%)	1677 (94.4)	1147 (91.5)	789 (93.6)	519 (90.4)	599 (42.0)	1125 (60.8)	5856 (75.8)
EFV based (%)	100 (5.6)	106 (8.4)	50 (5.9)	54 (9.4)	824 (57.7)	724 (39.1)	1858 (24.1)
Other (%)	0	1 (0.1)	4 (0.5)	1 (0.2)	4 (0.3)	1 (0.1)	11 (0.1)

EFV, efavirenz; NVP, nevirapine.

TABLE 3. Individual Patient Risk Factors for the 3 Outcomes Studied*

Patient Characteristics	No Follow-Up (n = 7714)		Mortality (n = 7265)		Loss to Follow-Up (n = 7265)	
	Odds Ratio (95% CI)†	P	Subhazard Ratio (95% CI)‡	P	Subhazard Ratio (95% CI)‡	P
Age (yrs)						
16–29	1	<0.001	1	0.08	1	<0.001
30–39	0.74 (0.58 to 0.95)		0.85 (0.69 to 1.04)		0.75 (0.65 to 0.86)	
≥40	0.58 (0.44 to 0.75)		1.03 (0.83 to 1.27)		0.53 (0.45 to 0.61)	
Sex						
Male	1	0.21	1	<0.001	1	0.003
Female	0.88 (0.71 to 1.08)		0.69 (0.59 to 0.80)		0.84 (0.75 to 0.94)	
Baseline CD4 cell count (cells/μL)						
0–49	1	<0.001	1	<0.001	1	<0.001
50–99	0.47 (0.30 to 0.75)		0.71 (0.55 to 0.93)		1.13 (0.91 to 1.40)	
100–199	0.59 (0.41 to 0.85)		0.57 (0.44 to 0.72)		0.82 (0.67 to 1.00)	
≥200	0.72 (0.52 to 1.01)		0.40 (0.31 to 0.52)		1.07 (0.88 to 1.30)	
Not measured	1.54 (1.11 to 2.13)		0.74 (0.58 to 0.94)		1.29 (1.06 to 1.57)	
Clinical stage						
WHO I–II	1	0.75	1	<0.001	1	0.83
WHO III–IV	0.96 (0.73 to 1.25)		1.80 (1.46 to 2.22)		1.01 (0.89 to 1.16)	
Calendar year of ART start						
Before 2008	1	0.05	1	<0.001	1	0.01
2008	0.89 (0.70 to 1.15)		0.76 (0.63 to 0.92)		1.15 (1.01 to 1.32)	
After 2008	1.23 (0.96 to 1.57)		0.66 (0.54 to 0.80)		1.26 (1.09 to 1.46)	
Country						
Lesotho	1	<0.001	1	<0.001	1	<0.001
Zimbabwe	1.02 (0.74 to 1.39)		0.47 (0.38 to 0.58)		0.57 (0.49 to 0.67)	
Mozambique	3.88 (2.88 to 5.23)		1.06 (0.85 to 1.32)		1.07 (0.90 to 1.26)	
Treatment regimen						
Nevirapin based	1	0.15	1	0.09	1	0.03
Efavirenz based	1.23 (0.93 to 1.62)		0.83 (0.67 to 1.03)		1.17 (1.02 to 1.35)	

*Adjusted for all variables shown in the table.

†Odds ratios from multivariable logistic regression.

‡Subhazard ratios from competing risk multivariable regression model.
CI, confidence interval.

3 years after the initiation of ART was unsatisfactory in all settings. Among patients followed up after the initial visit, mortality and LTFU were particularly high in young men and higher in Mozambique than in the other 2 countries.

The SolidarMed ART program serves poor, rural populations, in settings with little employment, low literacy and fragile, understaffed health systems. Indeed, one explanation for the poor retention is the limited capacity of the regional health systems, which were overwhelmed by the rapid scale-up of ART.⁸ This is illustrated by the 2 facilities in Mozambique as follows: in Chiure, staff was carefully trained and pre-ART counseling consistently implemented. These efforts generally translated into stable treatment partnerships. In contrast, the delivery of ART in Ancuabe started later and grew faster, initially without external support, and the training of staff was limited. Pre-ART counseling was not standardized and often not performed, leading to the initiation of treatment in patients who were ill prepared to take on the challenges of life-long ART. Structural factors and sociocultural factors have previously been linked to poor outcomes in ART programs.^{17–19}

Patients who do not come back to the health care facility after starting ART reflect a particular type of program failure. In our study, more than 5% of patients did not return after their first visit. Brinkhof et al⁸ found somewhat lower rates of early loss in the African programs included in the ART in Lower Income Countries collaboration; however, they mainly studied urban programs. Long-term retention was also low in our study, and particularly low in Lesotho and Mozambique where only 55% and 52% of patients, respectively, were alive and on ART at 3 years, fewer than the 72% estimated in the systematic review and meta-analysis of Fox et al.⁵ Again, most of the programs included in this review were from urban centers. A study of the barriers to accessing ART in Mozambique found that availability and cost of transport and clinic fees were major issues, particularly in rural areas, where the distance to the nearest clinic is large public transport limited and unemployment high.²⁰ In Lesotho, retention in care was below the estimates previously reported by Médecins sans Frontières in another setting in Lesotho. One explanation for this might be the large proportion of migrant workers to neighboring

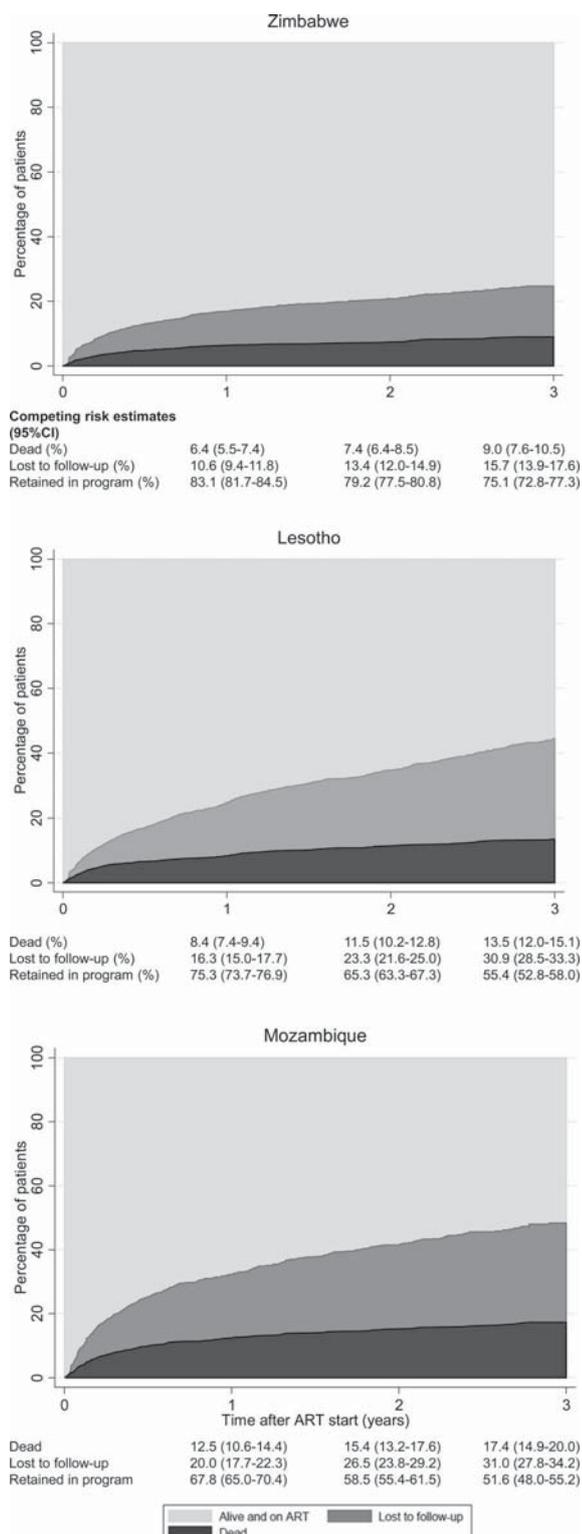


FIGURE 1. Cumulative probability of treatment outcomes after starting antiretroviral therapy in rural programs in Zimbabwe, Lesotho and Mozambique.

South Africa, a subpopulation known to be at higher risk of LTFU than the general population.^{21,22}

Patients lost to follow-up might reflect unaccounted self-referrals to other sites,²³ but this is unlikely in rural Mozambique and Zimbabwe, where ART is not widely available. In Lesotho, patients are routinely referred to peripheral health centers when clinically stable, but these patients will continue to be included in the common database. Men and patients younger than 30 years were more likely to be LTFU. Low retention in care of these groups is an important finding of our study and is consistent with other reports from Western, Eastern, and Southern Africa.^{7,8,24,25} Because patients in this age group are more likely to have no follow-up, be LTFU or to die than older patients, they warrant special attention and support from ART programs, both in urban and rural settings. The increasing proportion of patients lost to follow-up in recent years must be of concern. Even though it is difficult to attribute these changes to specific factors, the increasing number of patients needing treatment in each ART program in the context of weak health systems with poor organizational and logistic capacities probably had a major impact on the retention in care of patients on ART. The levels of staffing were extremely low in many of these health care facilities, contributing to the high proportions of patients lost or without any follow-up after the initiation of ART.

In the presence of LTFU, the mortality observed among patients remaining in care may substantially underestimate mortality in all patients starting ART because mortality in patients LTFU tends to be high. Several methods have been used to address this issue, including statistical modeling based on mortality in patients traced in Kenya, and linkage of HIV cohort records with the national death registry in South Africa.²⁶⁻²⁹ A nomogram and web calculator (implemented at www.iedea-sa.org) has also been developed, based on the fact that mortality of all patients starting ART is a weighted average of mortality among patients LTFU and patients remaining in care. When entering plausible estimates of mortality in patients LTFU from a meta-analysis,³⁰ we found mortality at 1 year increased to about 11% (from 6%) in Zimbabwe to about 15% (from 8%) in Lesotho and to about 19% (from 12%) in Mozambique.

The lack of access to viral load monitoring and second-line ART may have contributed to the high mortality. When comparing outcomes of ART in South Africa, where viral load monitoring is routine, with Malawi and Zambia, where monitoring is based on CD4 cell counts, we recently found that at 3 years more patients were on a failing first-line regimen, fewer patients had switched to second-line ART and mortality was higher in Malawi and Zambia than in South Africa.³¹ These observational data are in contrast with the results from a randomized clinical trial³² and a mathematical modeling study,³³ which showed no or little association between viral load monitoring and mortality. As none of the health facilities included in the present study had access to viral load monitoring, it was not possible to assess the potential effect of different monitoring strategies on ART outcomes directly in our study. Finally, mortality was higher in men and in those with CD4 cell counts below 50 cells per microliter

and advanced clinical stage, in line with the results of a prognostic model of patients starting ART in sub-Saharan Africa.³⁴

There are several limitations to our study. First, the mortality we observed in patients remaining in care is bound to be an underestimate of mortality at the level of the program. Unfortunately, the limited resources mean that patients LTFU cannot be consistently traced by outreach teams. We could therefore not provide accurate information on program-level mortality but estimated overall mortality based on published data on mortality in patients LTFU in sub-Saharan Africa.^{26,27} We did not systematically compare outcomes of rural programs with those located in urban areas, but such an analysis is planned within the IeDEA collaboration. No information was available on causes of death. Laboratory equipment was sometimes out of order or could not be operated because of power breaks or lack of reagents, resulting in a considerable number of patients with missing CD4 counts at baseline. This was especially true for Mozambique as follows: the programs either did not have a CD4 count device on site (Ancuabe) or faced frequent breakdowns of the device (Chiure). Severely ill and hospitalized patients were therefore started on ART without baseline CD4 count. Thus, the higher baseline CD4 counts in these 2 programs mainly relate to patients who were not hospitalized and in better health. Such selection bias was less important in Zimbabwe and Lesotho, where baseline CD4 count measurements seemed to be missing essentially at random.

In conclusion, our study illustrates some of the challenges rural ART programs face in sub-Saharan Africa. In particular, our results document the difficulties in retaining patients in care after they initiate ART and must raise concerns about poor long term clinical outcomes in settings with weak health systems and limited access to viral load monitoring and second-line ART regimens. Approaches to improve retention in care in such settings have been described recently, including reduction of the frequency of visits in patients who are stable, down referral of ART, and the involvement of peer support groups.^{12,35,36} Such interventions need to be tailored to local contexts and implemented alongside health systems strengthening initiatives.³⁷

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