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A Decade of Antiretroviral Therapy Scale-up in Mozambique: Evaluation of Outcome Trends and New Models of Service Delivery Among More Than 300,000 Patients Enrolled During 2004—2013

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Abstract

Background: During 2004–2013 in Mozambique, 455,600 HIV-positive adults (≥15 years old) initiated antiretroviral therapy (ART). We evaluated trends in patient characteristics and outcomes during 2004–2013, outcomes of universal treatment for pregnant women (Option B+) implemented since 2013, and effect on outcomes of distributing ART to stable patients through Community ART Support Groups (CASG) since 2010.

Methods: Data for 306,335 adults starting ART during 2004–2013 at 170 ART facilities were analyzed. Mortality and loss to follow-up (LTFU) were estimated using competing risks models. Outcome determinants were estimated using proportional hazards models, including CASG participation as a time-varying covariate.

Results: Compared with ART enrollees in 2004, enrollees in 2013 were more commonly female (55% vs. 73%), more commonly pregnant if female (,1% vs. 30%), and had a higher median baseline CD4 count (139 vs. 235/μL). During 2004–2013, observed 6-month mortality declined from 7% to 2% but LTFU increased from 24% to 30%. Pregnant women starting ART with

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CD4 count >350/μL and WHO stage I/II under Option B+ guidelines in 2013 had low 6-month mortality (0.1%) but high 6-month LTFU (38%). During 2010–2013, 6766 patients joined CASGs. In multivariable analysis, compared with nonparticipation in CASG, CASG participation was associated with 35% lower LTFU but similar mortality.

Conclusions: Initiation of ART at earlier disease stages in later calendar years might explain observed declines in mortality. Retention interventions are needed to address trends of increasing LTFU overall and the high LTFU among Option B+ pregnant women specifically. Further expansion of CASG could help reduce LTFU.

Keywords

antiretroviral therapy; Mozambique; trends; models of service delivery; community-based antiretroviral therapy delivery; Option B+

INTRODUCTION

Over the last decade, scale-up of antiretroviral therapy (ART) to reach more than 12 million persons living with HIV (PLHIV) in low- and middle-income countries (LMIC) has contributed to population-level reductions in mortality[1] and declines in HIV incidence.[2] In Mozambique, ranked 178th out of 187 countries on the Human Development Index, with <0.3 doctors per 10,000 population,[3] scale-up of ART to treat more than 800,000 PLHIV by 2016 is a highlight of global health achievements.[2] However, with >75% of HIV program funding coming from international donors[4] and plateaued international funding since 2009, Mozambique's ART program operates in a very resource-constrained environment, where monitoring of service quality and outcomes is especially important.[5,6] For example, an evaluation of Mozambique's national ART program during 2004–2007 reported concerning increases in rates of loss to follow-up (LTFU) and recommended future investigation of this trend.[7] In addition, Mozambique faces a new challenge in 2016 as it plans to phase in test-and-treat guidelines recommended by the World Health Organization (WHO),[8] which will further increase strain on health facilities as more patients become ART eligible.

Therefore, to inform future ART scale-up in this challenging environment, the Ministry of Health (MOH) and partners initiated a program evaluation to answer 3 primary questions: (1) what trends can be observed in ART patient characteristics and outcomes over the first decade of scale-up, (2) what lessons can be learned from Mozambique's experience implementing universal treatment for pregnant and breastfeeding women (Option B+) that might inform phased rollout of test-and-treat guidelines starting in 2016, and (3) can ART service delivery to stable patients on ART >6 months through Community ART Support Groups (CASGs) help reduce LTFU rates from the national ART program? Although incidence of LTFU among CASG participants was reported to be low in a small single-province pilot,[9,10] outcomes of the nation-wide pilot and the effect of CASG participation on LTFU in a comparative analysis have not yet been reported.

METHODS

ART Eligibility and Monitoring

Mozambique's ART guidelines changed over time (see Table, Supplemental Digital Content 1, http://links.lww.com/QAI/A862). There have been 3 guideline phases: 2004–2009, 2010–2012, and 2013–2016. During these phases, adults with WHO stage I/II were eligible if CD4 was ≤200, ≤250, and ≤350 cells per microliter, respectively.[11] In addition, since 2013, all HIV-infected pregnant women have been eligible for life-long ART through prevention of mother-to-child transmission Option B+ (referred to as Option B+ in this manuscript).[12]

At ART initiation, monthly for 4 months, at 6 months, and then semi-annually, patients attend clinician check-ups and standardized MOH-recommended records are completed. Most patients collect medications monthly from clinic pharmacies. For all patients late for monthly ART pick-up appointments, text messaging, followed by telephonic tracing, and if necessary, home visits, are recommended, but resource-limitations constrain tracing activities.

Community ART Support Groups

CASGs were first piloted in Tete province in 2008 to address increasing LTFU and alleviate patient-load on over-burdened clinics.[10] CASGs are groups of usually 6 patients, who take turns at monthly medication collections for the entire group, meaning that individual patients only attend the health facility semi-annually instead of monthly. To be CASG-eligible, adult ART patients must be stable, have taken ART for >6 months, have a CD4 >200 cells per microliter, and no active WHO stage III/IV conditions. A small pilot in Tete showed low LTFU among CASG participants,[9,10] and MOH expanded the pilot to 69 ART facilities nation-wide during 2010–2013.

Study Design and Population

This was an observational cohort study analyzing patient-level data prospectively entered into EPTS (a Microsoft Access database) by trained data clerks during 2004–2013. By December 2013, 170 of 288 adult ART facilities (60%) nationally were using EPTS covering 67% of all ART patients. Built-in consistency and legal range checks help maintain EPTS data quality. Semi-annually, data are transferred to a central data warehouse, co-managed by MOH and other stakeholders for further quality checks, data set concatenation, and data management.

For this analysis, only adults ≥15 years old at ART initiation, who started ART during 2004–2013, were eligible. Facility-level databases were closed in April 2014.

Treatment Outcomes

Primary ART outcomes were mortality and LTFU, whereas attrition (documented death or LTFU) was a secondary outcome.[13] Per Mozambique standards, patients were considered LTFU if ≥60 days late for their next scheduled medication pick-up appointment. Mortality ascertainment occurred through passive reporting, and through MOH-recommended tracing activities.

Exposure Variables

Exposure variables are listed in Tables 1 and 2. Sex was coded as a 3-level variable (male, nonpregnant female, and pregnant female).[14] Rate of site expansion was coded as patient rank divided by site-specific duration of ART services (eg, for a site's 100th ART enrollee, enrolled 4 months after ART service initiation, the expansion rate is 25).[6] For each site, size was defined by calendar year as the number of current ART enrollees by calendar year end.[6]

Analytic Methods

Data were analyzed using STATA 13 (StataCorp, 2009, Stata Statistical Software, Release 13, College Station, TX).

Complete data were available for time-to-event analysis and for key exposure variables, including ART initiation year, CASG participation, age, sex, site expansion, and site size. For certain other variables (Tables 1 and 2), some data were missing.

To best manage missing covariate data, multiple imputation is preferred to complete case analysis,[15,16] because complete case analysis can yield biased parameter estimates.[16] First, patterns of missing data were explored using the "mi misstable patterns" command to assess plausibility of the missing at random assumption. Although the missing at random assumption cannot be proven, it was considered plausible for this analysis. Therefore, the mi[17] procedure in STATA was used to create 20 imputed data sets for each outcome (death and LTFU) separately.[7] Missing covariate data were only imputed if <35% of data were missing. For all analyses using imputed data, estimates were combined across imputed data sets according to Rubin's rules.[18] Intrafacility correlation was accounted for using the generalized Huber/White/sandwich estimator of robust standard errors.[19,20]

To evaluate trends in patient characteristics over time, associations between baseline characteristics and ART initiation year were assessed using regression models appropriate for variable type. To evaluate outcome trends over time, competing risk models were used to estimate mortality and LTFU for each annual cohort of ART enrollees during 2004–2013.[13,21–23] Because a nationally representative study to ascertain vital status of patients LTFU has not yet been implemented, a published nomogram, based on a meta-regression analysis of 15 LTFU tracing studies from sub-Saharan Africa, was used to estimate true 1-year mortality incidence for each annual cohort.[24]

To evaluate outcome determinants, proportional hazards regression models were used to estimate adjusted hazard ratios (AHRs).[13,22] Multivariable models were adjusted for covariates considered a priori risk factors: year of ART initiation, age, sex, marital status, number of children, education, employment, referral source, WHO stage, baseline weight, baseline CD4, patient's CASG participation, site-level availability of CASG, rate of site expansion, site size, and ART regimen. CASG participation after ART initiation was coded as time-varying in multivariable models to avoid survivor bias, per published precedent.[25] The proportional hazards assumption was assessed using visual methods and the Grambsch and Therneau test.

Ethics Approval

Use of routine, anonymized data for this study was approved by the Mozambican Ethics Committee and the Center for Global Health Science Office at the Centers for Disease Control and Prevention.

RESULTS

Trends in Patient Characteristics at ART Initiation

During 2004–2013, 306,335 adults initiated ART at facilities with EPTS. Annual adult ART enrollment rates increased 37-fold from 1784/year in 2004 at 9 facilities to 65,442/year in 2013 at 170 facilities. During 2004–2013 at ART enrollment, the percentage who were male declined from 45% to 27% and the percentage who were nonpregnant females from 55% to 51%, whereas the percentage who were pregnant females increased from 0.3% to 22% ($P < 0.001$), with the steepest increase occurring during 2012–2013 (from 10% to 22%) (Table 1). In 2013, following initiation of Option B+, pregnant females with CD4 count >350 cells per microliter and WHO stage I/II represented 8% of all 2013 enrollees, 11% of all females, and 35% of all pregnant females (up from 0% in 2004). The female-to-male ART enrollee ratio increased from 1.2 to 2.7 during 2004–2013.

Median age at ART enrollment declined from 35.9 in 2004 to 31.1 years in 2013 ($P < 0.001$). In each calendar year, median age of pregnant female ART enrollees was lower than that of nonpregnant females and males (Table 1). During 2004–2013, the percentage referred after HIV testing and counseling (HTC) at health facilities decreased from 68% to 34%, whereas the proportion referred from antenatal care (ANC) increased from 0% to 24% ($P < 0.001$) with the steepest annual increase occurring during 2012–2013 (from 12% to 24%).

Median time from HIV diagnosis to ART initiation declined substantially from 4.27 to 0.46 years during 2004–2013 ($P < 0.001$) with declines similar for males, nonpregnant females, and pregnant females (Table 2). WHO stage IV prevalence at ART initiation declined from 28% to 4% during 2004–2013 ($P < 0.001$). Median CD4 at ART initiation increased from 139 to 235 per microliter during 2004–2013 ($P < 0.001$), with increases most pronounced for pregnant females (81–309 per microliter) compared with males (129–187 per microliter) and nonpregnant females (150–231 per microliter) (Table 2).

During 2004–2009, stavudine, lamivudine, and nevirapine were the most common regimens, accounting for 73%–88% of regimens (see Figure and Table, Supplemental Digital Content 2, http://links.lww.com/QAI/A921). However, during 2010–2012, zidovudine, lamivudine, and nevirapine became more common, accounting for 58%–81% of regimens. During 2012–2013, increased tenofovir, lamivudine, and efavirenz use was noted for males (from 0% to 12%), nonpregnant females (from 0% to 16%), and pregnant females (from 0% to 40%). During 2004–2013, stavudine use declined from 92% to 7%, whereas zidovudine and tenofovir use increased from 5% to 71% and 0%–20%, respectively. Nevirapine use declined from 91% to 63%, whereas efavirenz use increased from 6% to 35%.

CASG Participants

During 2010–2013, 6766 patients joined a CASG at 69 ART facilities. Compared with non-CASG participants, CASG participants were more likely to be female (67% vs. 76%, $P < 0.001$), be older at ART enrollment (median age 33.0 vs. 36.2 years, $P < 0.001$), have no education (13% vs. 21%, $P < 0.001$), be unemployed (68% vs. 77%, $P = 0.033$), and have had a longer time from diagnosis to ART initiation (1.48 vs. 4.34 years, $P < 0.001$) (Table 3). However, at ART enrollment, WHO stage IV disease prevalence (10% vs. 8%, $P = 0.315$) and median CD4 count (182 vs. 195 per microliter, $P = 0.463$) were similar between participants and nonparticipants in CASG. Twenty percent of CASG enrollees joined CASG in months 0–12, 23% in months 12–24, and 58% after 24 months of ART.

Trends in Outcomes

Over 517,608 years of ART follow-up, 26,910 (9%) patients transferred out, 113,420 (37%) were LTFU, and 16,486 (5%) died. Overall, documented mortality was 4% and LTFU 27% at 1 year of follow-up. After correcting for estimated rates of undocumented mortality among those LTFU, corrected 1-year mortality was about 13% and corrected LTFU 18% (see Table, Supplemental Digital Content 3, http://links.lww.com/QAI/A922).

During 2004–2013, observed 6-month mortality declined from 7% to 2% but LTFU increased from 24% to 30% (Table 4). Similarly, during 2004–2012, documented 1-year mortality declined from 9% to 3%, but 1-year LTFU increased from 26% to 31%. Corrected 1-year mortality declined from about 17% among 2004 enrollees to about 13% among 2012 enrollees, whereas corrected 1-year LTFU increased from about 18% to 21% (see Table, Supplemental Digital Content 3, http://links.lww.com/QAI/A922).

After 9 years of ART for 2004 enrollees, 13% had died and 51% were LTFU, giving overall retention of 37% (Table 4).

In bivariate regression, more recent year of ART initiation was predictive of lower documented mortality rates, (See Table, Supplemental Digital Content 4, http://links.lww.com/QAI/A923). However, in multivariable analysis, no statistically significant association between year of ART initiation and mortality was observed (Table 5). In contrast, later calendar year of ART initiation was associated with higher LTFU in both crude and multivariable analyses (Table 5).

CASG Outcomes

Among CASG participants, incidence of death after ART initiation was 0.3% at 2 years and 1.4% at 4 years, whereas LTFU incidence was 2.9% at 2 years and 10.1% at 4 years. After controlling for confounders (all variables listed in Table 5), and introducing CASG participation as a time-varying covariate to avoid survivor bias, compared with nonparticipation in CASG, CASG participation was associated with 35% lower LTFU rates [AHR 0.65, 95% confidence interval (CI), 0.46–0.91], but similar mortality (Table 5). In sensitivity analyses, restricting the cohort to the 128,364 enrollees starting ART during 2010–2013 at only those 69 clinics offering CASG programs, CASG participation was

associated with 55% reduced LTFU rates (AHR 0.45, 95% CI: 0.32 to 0.64), but similar mortality (See Table, Supplemental Digital Content 5, http://links.lww.com/QAI/A924).

Option B+ Outcomes

In 2013, 6-month mortality was lowest among the Option B+ group of pregnant women enrolled with CD4 >350 cells per microliter and WHO stage I/II (0.1%), compared with other pregnant ART enrollees (1%), nonpregnant females (3%), and males (5%); however, 6-month LTFU was highest for the Option B+ group (38%), compared with other pregnant ART enrollees (26%), nonpregnant females (18%), and males (23%).

Other Outcome Predictors

In multivariable analysis, compared with nonpregnant females, males had higher LTFU and mortality, and pregnant females had higher LTFU but lower mortality (Table 5).

In multivariable analysis, compared to patients with CD4 <50/μL at ART initiation, patients with CD4 counts between 50/μL and 500/μL had 7%–15% lower LTFU (Table 5). However, LTFU rates were similar between those with CD4 <50/μL (23.9/100 person-years) and CD4 >500/μL (32.0/100 person-years). In contrast, compared to patients with CD4 <50 μL, all patients with higher CD4 counts had 36%–54% lower mortality (Table 5). Other markers of advanced disease (ie, advanced WHO stage and low weight at ART initiation) were predictive of both LTFU and mortality (Table 5).

Compared with zidovudine-containing regimens, stavudine-containing regimens had 48% higher mortality, but similar LTFU. Compared with nevirapine-containing regimens, efavirenz-containing regimens had 9% higher LTFU but similar mortality, whereas protease inhibitor-containing regimens had 29% higher LTFU but similar mortality. AHRs derived using the multiple imputation approach were similar to AHRs derived using a complete case analysis approach (See Table, Supplemental Digital Content 6, http://links.lww.com/QAI/A925).

DISCUSSION

With a cohort size of 306,335, this is the largest single-country cohort of adult ART enrollees described to date.[26] The analysis is timely in that it exemplifies a key success (ie, declines in observed ART mortality rates), a key challenge for the future (ie, increases in observed LTFU rates), and a potential partial solution to address the problem of increasing LTFU (ie, ART distribution through CASG). Other notable findings include the high 6-month LTFU among Option B+ enrollees with CD4 >350 cells per microliter and WHO stage I/II at ART initiation and the high LTFU rates among patients starting ART with CD4 >500 cells per microliter. Both these findings have implications for Mozambique as it begins to pilot test-and-treat in 2016.

Similar to other studies in LMIC,[5,6,26] observed ART mortality rates were lower among enrollees in more recent calendar years compared with enrollees in earlier years. Since in crude analysis, later year of ART initiation was associated with lower observed mortality rates, but in multivariable analysis, this association disappeared, changes in patient

characteristics at ART initiation over calendar time (eg, declining percentage of enrollees who were male, declining prevalence of CD4 <50/μL and declining stavudine use), explain, at least partly, the declining ART mortality in our analysis. Since 20%–60% of patients LTFU from ART are likely to have died,[27] we used a published nomogram to explore whether a trend of declining 1-year ART mortality was still present after correcting for estimated undocumented death. Point estimates of corrected 12-month mortality declined from 17% in 2004 to 13% in 2012, but nomogram-generated 95% CIs for these estimates overlapped. Although observed data suggest that ART mortality has declined during 2004–2013, a tracing study to ascertain outcomes of patients LTFU is needed, and is planned, to confirm these findings.

Given the association between patient characteristics at ART initiation and outcomes, understanding patient characteristics and changes over time is important for program managers. The increasing female-to-male ART enrollee ratio from 1.2 to 2.7 during 2004–2013 was probably due to scale-up of HTC at ANC and Option B+ initiation in 2013 and is not explained by slight increases in population-level female-to-male ratios among PLHIV (from 1.43 to 1.49).[28,29] As discussed in depth separately,[29] increased ART enrollment among men is needed to reduce disproportionately high HIV-related morbidity and mortality among men[30] and reduce HIV incidence among their sexual partners.[29] Increases in median CD4 count at ART initiation, and declining prevalence of WHO stage IV, similar to other reports,[5,31–33] probably reflect expanded HTC, ART access, and ART eligibility. Expanding ART access and ART eligibility are also reflected in the remarkable declines in time from HIV diagnosis to ART initiation during 2004–2013. However, more rapid average annual increases in median baseline CD4 for nonpregnant females (9.1 cells · μL−1·yr−1) and pregnant females (25.3 cells·μL^{-1}·yr^{-1}) compared with males (6.4 cells·μL^{-1}·yr^{-1}) suggest ART access increased more rapidly for females than males. This highlights the importance of ANC HTC and Option B+ as gateways to early ART for females, and the need to identify gateways that work for men.[34]

Due to stavudine-induced severe adverse events, WHO recommended stavudine phase-out in 2009.[35] Mozambique responded rapidly with significant declines in first-line stavudine prescription during 2009–2010, and by 2013, only 7% of adults started stavudine-containing first-line regimens. This study contributes new evidence that, compared with zidovudine, first-line stavudine-containing regimens carry mortality risk.[26,35] Complete stavudine phase-out is required, especially since costs of tenofovir and zidovudine have declined substantially.[36]

Similar to prior Mozambique analyses[7] and other studies from LMIC,[6,37,38] observed ART LTFU rates increased over time, being nearly 3-fold higher among 2013 enrollees than 2004 enrollees. Unlike the mortality analysis, later calendar year of ART initiation was associated with higher LTFU in both crude and adjusted regression, suggesting that unmeasured factors associated with calendar time explain increasing LTFU. With only 3 pharmacy staff per 100,000 people, the increasing patient-to-pharmacist ratio has been cited as a cause for increasingly long clinic wait times for ART patients,[39] resulting in patient dissatisfaction and LTFU.[39–41] Per precedent,[42] we used rate of site expansion and site size as proxy variables for patient-to-provider ratios, but our proxy variables were not important

explanatory variables in the LTFU regression. One explanation, as reported previously,[39] is that patient-to-provider ratios do not correlate with pharmacist-to-patient ratios, which may be the underlying site-level factor determining LTFU rates.[39] Alternately, other factors might explain increasing LTFU such as increasing undocumented transfer between health facilities or declines in recordkeeping quality.[43,44] In addition, a recent model-based analysis reported that treatment interruptions are more likely to be misclassified as LTFU in recent cohorts compared with early cohorts, and this might explain some of the observed increases in LTFU rates over time.[44] This highlights the need for an LTFU tracing study, which could help to identify drivers of LTFU and help determine to what extent observed LTFU is true LTFU.[45]

By including CASG participation as a time-varying covariate and controlling for confounders, this is the first attempt to quantify effect of CASG participation on LTFU rates and the first nation-wide report of CASG outcomes.[9,10] This analysis complements a separately described propensity score-matched cohort analysis; both analytic approaches observed a statistically significant LTFU reduction associated with CASG participation. For both analytic approaches, a limitation is that agreeing to join a CASG might be correlated with better health-seeking behavior, which might result in better retention regardless of CASG participation.[9] For example, CASG participants had a longer median time from HIV diagnosis to ART initiation, which might suggest they sought HIV testing earlier than nonparticipants, a possible indicator of health-seeking behavior. However, considering that CASG scale-up carries other benefits for the ART program, including decongestion of ART facilities and reduced burden on providers,[9,46] and appears to be highly preferred by most CASG participants,[46] these findings warrant continued CASG scale-up. Since these data were analyzed, CASG scale-up has continued and by April 2016, about 64,932 (8%) of all 802,659 patients were enrolled in CASGs nation-wide.

Notably, CASG participants were more commonly unemployed and uneducated than nonparticipants, which might indicate that CASG participation is more attractive for patients with fewer financial resources.[9,10] This makes intuitive sense since key patient benefits of CASG participation, as reported by CASG participants, are the cost- and time-savings associated with biannual rather than monthly clinic attendance.[46] Low male uptake of CASG warrants further research. Offering male-only CASGs might improve male participation in CASG.[47] Alternately, other service delivery models that emphasize privacy might be preferred by some stable male patients.[48] Possible reasons for lower LTFU following CASG participation include reduced patient transport costs, reduced patient time at the clinic, increased patient accountability, and improved social support.[10] Given the shortage of healthcare workers, task-shifting to patients might be a cornerstone of future ART expansion and sustained ART coverage in Mozambique and similar LMIC.[10,49–53]

Similar to recent program data from South Africa[54] and Canada,[55] but in contrast to research cohort data from LMIC,[42] ART initiation at CD4 >500/μL was associated with LTFU.[42] In our programmatic setting, patients who feel healthy at ART initiation and experience dissatisfaction with monthly ART refills at crowded facilities might be at higher LTFU risk than those who feel sicker.[56–58] Further research to understand LTFU causes among patients with CD4 >500/μL at ART initiation is needed to inform test-and-treat rollout in a way that maximizes patient health and HIV prevention benefits.[8,56]

Similar to most reports,[59–61] pregnancy at ART initiation was associated with higher LTFU but lower mortality. In contrast to pregnant females, who were mostly referred from routine HTC at ANC, nonpregnant women were largely referred from clinics and VCT centers where they were seeking healthcare at the time of diagnosis. Therefore, inferior motivation for life-long ART might explain higher LTFU among pregnant versus nonpregnant enrollees.[62] Other barriers to ART retention among pregnant women might include declining motivation to stay on ART post-partum, new financial constraints, new childcare responsibilities, post-partum depression, and navigating complex referral pathways.[62]

Our 6-month LTFU among Option B+ enrollees with CD4 >350 and WHO stage I/II at ART initiation (38%) is much higher than reports from Malawi (17%).[63] However, similar to Malawi, the Option B+ group had higher LTFU than pregnant woman starting ART per national standards at CD4 ≤350 or WHO stage III/IV.[63] Our analysis suggests that high CD4 count at ART initiation, which may be associated with "feeling healthy," might partly explain higher LTFU in the prevention of mother-to-child transmission B+ group compared with other pregnant ART enrollees, but further research is needed.[64] Models of Option B+ that facilitate retention are urgently needed.

Strengths of the analysis include the large cohort size, number of clinics included (170), duration of observation (10 years), and proportion of Mozambique's adult ART population captured (67%). As with all observational studies, some associations might be confounded by unmeasured confounders. For example, the association between efavirenz use and LTFU might be confounded by higher likelihood of prescribing efavirenz-based regimens to TB co-infected enrollees.[26] Other limitations include the fact that findings are limited to clinics with EPTS and the possibility that missing covariate data introduced nondifferential measurement error. In addition, despite MOH-recommended tracing efforts, reported LTFU rates are probably overestimates and observed mortality rates underestimates because of incomplete death documentation.[27]

CONCLUSIONS

Mozambique's rapid expansion of ART access is a significant national and global health achievement. This analysis suggests that initiation of better ART regimens at earlier disease stages in later calendar years at least partly explains declining ART mortality. However, LTFU rates increased over time and interventions to reverse this trend are needed. Further scale-up of CASG is one intervention to help reverse trends of increasing LTFU. In addition, targeted LTFU prevention strategies to address high LTFU among pregnant women overall, Option B+ enrollees specifically, and all patients starting ART with CD4 >500/μL are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1.

Trends in Demographic Characteristics of Adult ART Enrollees in Mozambique During 2004–2013

	Full Cohort (Unimputed)		Annual ART Cohorts*									
	n	% or median	2004 (n = 1784)	2005 (n = 4694)	2006 (n = 12,634)	2007 (n = 25,616)	2008 (n = 26,704)	2009 (n = 31,129)	2010 (n = 37,449)	2011 (n = 41,991)	2012 (n = 58,892)	2013 (n = 65,442)
Sex												
Male	100,333	33%	45%	41%	39%	36%	36%	35%	34%	33%	32%	27%
Nonpregnant female	175,258	57%	55%	57%	59%	59%	58%	59%	59%	59%	58%	51%
Pregnant female	30,744	10%	0.3%	2%	2%	5%	5%	5%	7%	9%	10%	22%
Age at ART start, median												
(IQR), yrs†												
Overall		33.1	35.9	36.0	35.1	34.0	34.0	34.0	34.0	33.2	33.1	31.1
Male		37.0	38.4	39.2	38.0	37.3	37.2	37.1	37.1	36.7	36.3	35.9
Nonpregnant female		32.6	33.5	33.8	33.5	32.8	32.6	32.9	33.0	32.7	32.7	32.0
Pregnant female		26.3	29.4	27.3	27.5	27.1	27.1	27.3	27.1	27.0	27.0	25.5
Age categories												
15 to <20	10,485	3%	1%	1%	2%	3%	3%	2%	2%	3%	3%	7%
20 to <25	38,533	13%	8%	7%	9%	11%	11%	11%	11%	12%	12%	16%
25 to <30	60,910	20%	19%	18%	18%	19%	20%	19%	19%	20%	20%	21%
30 to <40	106,882	35%	37%	37%	36%	35%	35%	36%	36%	35%	35%	33%
40 to <60	81,639	27%	33%	34%	32%	29%	29%	29%	29%	27%	26%	21%
≥60	7886	3%	2%	2%	2%	2%	2%	3%	3%	3%	3%	2%
Marital status												
Married	31,849	12%	22%	16%	16%	15%	14%	13%	11%	10%	11%	12%
Single	99,540	38%	53%	40%	42%	40%	39%	38%	38%	39%	39%	38%
Civil union	106,710	41%	17%	34%	31%	35%	37%	40%	42%	43%	43%	44%
Widowed/divorced	20,975	8%	8%	10%	11%	10%	9%	9%	9%	8%	7%	6%
Missing	47,261	15%										
No. biological children												
0	34,165	14%	27%	33%	25%	25%	21%	19%	15%	11%	9%	9%

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	Full Cohort (Unimputed)		Annual ART Cohorts*									
	n	% or median	2004 (n = 1784)	2005 (n = 4694)	2006 (n = 12,634)	2007 (n = 25,616)	2008 (n = 26,704)	2009 (n = 31,129)	2010 (n = 37,449)	2011 (n = 41,991)	2012 (n = 58,892)	2013 (n = 65,442)
1–2	99,969	41%	35%	31%	34%	36%	37%	39%	41%	43%	43%	45%
≥3	111,210	45%	38%	37%	41%	40%	41%	42%	45%	46%	48%	46%
Missing	60,991	20%										
Education												
None	28,606	12%	6%	7%	10%	12%	12%	13%	13%	14%	14%	14%
Primary	143,102	62%	53%	58%	62%	65%	64%	64%	63%	63%	62%	60%
Secondary	55,664	24%	38%	32%	26%	22%	22%	22%	22%	23%	23%	25%
University	3454	1%	3%	3%	2%	2%	2%	2%	1%	1%	1%	1%
Missing	75,509	25%										
Employment												
Employed	64,340	26%	49%	45%	38%	30%	29%	29%	29%	28%	27%	22%
Unemployed	170,683	69%	45%	50%	57%	65%	67%	67%	67%	68%	69%	73%
Student	10,945	4%	6%	6%	5%	4%	5%	5%	5%	4%	4%	4%
Missing	60,367	20%										
Referral source												
HC referral	121,034	40%	68%	35%	37%	38%	41%	40%	42%	43%	42%	34%
VCT	121,865	40%	18%	44%	48%	46%	42%	44%	41%	39%	38%	35%
ANC/PMTCT	37,098	12%	0%	1%	2%	6%	7%	7%	9%	12%	12%	24%
TB clinic	7132	2%	0%	0%	1%	2%	2%	2%	2%	3%	3%	3%
Other	19,061	6%	14%	20%	10%	8%	8%	6%	5%	5%	5%	5%
Missing	145	0%										

*Estimates for annual cohorts are from imputed data sets; estimates derived from unimputed data were very similar. *P*-values for statistical tests evaluating the significance of trends over time were all <0.001.

†Cubic polynomials for year of ART initiation were included in the linear regression model since *P*-values for the cubic and unmodified ART year coefficients were <0.05 and their signs opposite.

HC, health center; IQR, interquartile range; no., number; PMTCT, prevention of mother-to-child transmission; TB, tuberculosis; VCT, voluntary counseling and testing.

TABLE 2.

Trends in Clinical Characteristics of Adult ART Enrollees in Mozambique During 2004–2013

	Full Cohort (Unimputed)		Annual ART Cohorts*									
	n	% or median	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Time from HIV diagnosis to treatment, median (IQR), yr†												
Overall	259,840	1.55	4.27	4.09	3.45	3.06	2.60	3.20	2.93	2.13	1.31	0.46
Male	84,165	1.33	3.34	3.86	2.91	2.23	1.96	2.45	2.52	1.93	1.17	0.43
Nonpregnant female	147,102	1.83	4.65	4.25	3.70	3.50	3.09	3.61	3.07	2.23	1.40	0.55
Pregnant female	28,573	0.79	4.89	5.34	4.07	3.40	2.65	3.69	2.99	2.09	1.25	0.30
Missing	46,495	15%										
WHO stage												
I	76,685	33%	9%	10%	12%	15%	16%	21%	29%	35%	38%	50%
II	52,260	22%	13%	15%	17%	18%	20%	23%	25%	24%	25%	21%
III	82,044	35%	50%	52%	52%	49%	47%	43%	37%	33%	31%	25%
IV	21,372	9%	28%	23%	20%	18%	17%	13%	9%	8%	6%	4%
Missing	73,974	24%										
Weight categories, kg												
<45	33,333	16%	15%	17%	19%	20%	20%	19%	17%	17%	16%	15%
45–60	120,535	58%	51%	52%	54%	56%	55%	56%	55%	55%	55%	57%
>60	52,667	26%	34%	31%	27%	24%	24%	25%	28%	28%	29%	29%
Missing	99,800	33%										
CD4 count median, cells/μL‡												
Overall	208,683	185	139	124	138	144	151	158	170	185	213	235
Male	69,085	158	129	111	122	128	134	140	145	159	182	187
Female	121,221	189	150	133	146	148	156	163	177	191	219	231
Pregnant female	18,377	261	81	169	199	212	204	211	227	242	265	309
Missing	97,652	32%										
CD4 count category, cells/μL												
<50	28,226	14%	21%	23%	20%	18%	17%	16%	14%	13%	11%	9%
50–200	86,194	41%	45%	50%	50%	51%	50%	48%	46%	42%	36%	33%

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	Full Cohort (Unimputed)		Annual ART Cohorts*									
	n	% or median	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
201–350	71,741	34%	22%	20%	22%	24%	25%	28%	31%	35%	39%	35%
351–500	12,862	6%	7%	4%	5%	5%	5%	5%	6%	6%	9%	13%
>500	9660	5%	6%	2%	3%	2%	2%	3%	3%	4%	5%	11%
Missing	97,652	32%										

*Estimates for annual cohorts are from imputed data sets; estimates derived from unimputed data were very similar. *P*-values for statistical tests evaluating the significance of trends over time were all <0.001.

†Cubic polynomials for year of ART initiation were included in the linear regression model since *P*-values for the cubic and unmodified ART year coefficients were <0.05 and their signs opposite.

‡Quadratic terms for year of ART initiation were included in the linear regression model since *P*-values for the quadratic and unmodified ART year coefficients were <0.05 and their signs opposite.

IQR, interquartile range.

TABLE 3.

Comparison of ART Initiation Characteristics Between CASG Participants and Nonparticiapants

	Nonparticipants in CASG (N = 299,569)	CASG Participants (N = 6766)	*P* *
Sex, %			
Male	33	24	<0.001
Nonpregnant female	57	70	
Pregnant female	10	6	
Age at ART start, yrs			
Median (IQR)	33.0 (27.2–41.4)	36.2 (30.0–44.2)	<0.001
Marital status, %			
Married	12	14	0.739
Single	47	43	
Civil union	41	43	
No. biological children, %			
0 children	14	16	0.055
1–2 children	41	34	
≥3 children	44	50	
Education, %			
None	13	21	<0.001
Primary	62	64	
Secondary	23	14	
University	1	0	
Employment, %			
Employed	28	20	0.033
Unemployed	68	77	
Student	4	3	
Referral source, %			
HC referral	40	34	0.433
VCT	40	50	
ANC/PMTCT	12	8	
TB clinic	2	2	
Other	6	5	
Time from HIV diagnosis to treatment Median (IQR), yr	1.48 (0.42–3.33)	4.34 (3.04–5.77)	<0.001
WHO stage, %			
I	32	27	0.315
II	22	26	
III	36	40	
IV	10	8	
Weight categories, kg			
<45	17	17	0.176
45–60	55	58	
>60	28	25	

	Nonparticipants in CASG (N = 299,569)	CASG Participants (N = 6766)	*P* *
CD4 Count, cells/μL			
Median (IQR)	182 (93–280)	195 (114–271)	0.463

* *P*-value derived from logistic regression model with CASG participation as the dependent variable of interest.

PMTCT, prevention of mother-to-child transmission; HC, health center; IQR, interquartile range; TB, tuberculosis; VCT, voluntary counseling and testing.

TABLE 4.

Incidence of Death and LTFU by Calendar Year of ART Initiation

		ART Enrollment Year									
	Years After ART Initiation	**2004, %**	**2005, %**	**2006, %**	**2007, %**	**2008, %**	**2009, %**	**2010, %**	**2011, %**	**2012, %**	**2013, %**
Death	0.5	7	5	6	5	4	4	4	3	2	2
	1	9	6	7	6	6	5	5	4	3	
	2	10	7	9	8	7	7	6	5		
	3	11	9	10	9	8	8	6			
	4	11	9	11	10	9	8				
	5	11	10	11	10	10					
	6	12	11	12	11						
	7	12	11	12							
	8	13	11								
	9	13									
LTFU	0.5	24	18	20	21	22	17	15	18	20	30
	1	26	21	23	25	26	21	20	24	31	
	2	28	24	28	30	32	28	29	37		
	3	29	28	32	34	36	33	39			
	4	33	31	35	37	40	41				
	5	37	35	38	41	46					
	6	40	38	42	47						
	7	42	42	47							
	8	45	46								
	9	51									
Retention (Alive on ART)	0.5	69	77	74	74	74	79	81	79	78	68
	1	65	73	70	69	68	73	75	72	66	
	2	61	68	63	62	61	66	66	59		
	3	60	63	59	58	56	59	55			
	4	56	60	55	53	51	50				
	5	52	55	51	48	44					
	6	48	52	46	42						

Years After ART Initiation	ART Enrollment Year									
	2004, %	2005, %	2006, %	2007, %	2008, %	2009, %	2010, %	2011, %	2012, %	2013, %
7	45	47	40							
8	42	43								
9	37									

LTFU, lost to follow-up; ART, antiretroviral therapy.

TABLE 5.

Predictors of LTFU and Death Among Adults Initiating Antiretroviral Therapy in Mozambique During 2004–2013

	Original	LTFU				Death			
	n	Rate/100PY	AHR	95% CI	*P*	Rate/100PY	AHR	95% CI	*P*
Year of ART initiation									
2004	1784	11.0	—	—	—	2.9	1.00	—	—
2005	4694	10.2	0.92	0.72 to 1.16	0.471	2.7	0.92	0.41 to 2.04	0.832
2006	12,634	12.1	1.09	0.89 to 1.34	0.410	3.3	1.08	0.41 to 2.82	0.879
2007	25,616	13.6	**1.25**	**1.02 to 1.53**	**0.033**	3.1	0.94	0.34 to 2.60	0.906
2008	26,704	15.9	**1.43**	**1.15 to 1.77**	**0.001**	3.2	0.91	0.32 to 2.55	0.852
2009	31,129	15.9	**1.42**	**1.06 to 1.91**	**0.018**	3.1	0.85	0.29 to 2.47	0.770
2010	37,449	18.7	**1.63**	**1.12 to 2.36**	**0.011**	2.9	0.92	0.32 to 2.68	0.884
2011	41,991	25.7	**1.98**	**1.30 to 3.01**	**0.001**	2.9	0.89	0.31 to 2.60	0.832
2012	58,892	39.5	**2.45**	**1.55 to 3.86**	**<0.001**	3.1	0.76	0.26 to 2.23	0.617
2013	65,442	77.7	**2.73**	**1.59 to 4.67**	**<0.001**	4.6	0.65	0.22 to 1.91	0.437
Age category									
15 to <20	10,485	45.7	1.00	—	—	4.1	1.00	—	—
20 to <25	38,533	31.8	**0.84**	**0.80 to 0.88**	**<0.001**	3.5	0.97	0.86 to 1.09	0.592
25 to <30	60,910	24.5	**0.70**	**0.66 to 0.74**	**<0.001**	3.1	**0.87**	**0.77 to 1.00**	**0.043**
30 to <40	106,882	19.8	**0.60**	**0.56 to 0.64**	**<0.001**	2.8	**0.80**	**0.70 to 0.92**	**0.001**
≥40	89,525	16.7	**0.53**	**0.49 to 0.57**	**<0.001**	4.1	0.93	0.80 to 1.09	0.381
Sex									
Nonpregnant females	175,258	18.6	1.00	—	—	2.4	1.00	—	—
Males	100,333	24.5	**1.49**	**1.42 to 1.55**	**<0.001**	4.9	**1.92**	**1.82 to 2.02**	**<0.001**
Pregnant females	30,744	31.8	**1.11**	**1.00 to 1.22**	**0.049**	1.1	**0.81**	**0.69 to 0.94**	**0.007**
Marital status									
Married	138,559	20.6	1.00	—	—	3.0	1.00	—	—
Single	99,540	24.0	**1.13**	**1.06 to 1.20**	**<0.001**	3.3	**1.08**	**1.02 to 1.13**	**0.003**
Widowed/divorced	20,975	15.4	1.00	0.96 to 1.03	0.835	2.5	0.98	0.91 to 1.05	0.503
No. biological children									
0 children	34,165	22.2	1.00	—	—	3.8	1.00	—	—

	Original	LTFU				Death			
	n	Rate/100PY	AHR	95% CI	*P*	Rate/100PY	AHR	95% CI	*P*
1–2 children	99,969	23.9	**0.94**	**0.89 to 1.00**	**0.037**	3.0	**0.85**	**0.77 to 0.94**	**0.001**
≥3 children	111,210	18.9	**0.88**	**0.82 to 0.94**	**<0.001**	2.9	**0.82**	**0.73 to 0.91**	**<0.001**
Education level									
None	28,606	22.4	1.00	—	—	3.3	1.00	—	—
Primary	143,102	21.1	**0.91**	**0.86 to 0.96**	**0.001**	3.1	0.99	0.92 to 1.07	0.845
Secondary	55,664	21.3	**0.85**	**0.79 to 0.91**	**<0.001**	3.0	0.98	0.89 to 1.08	0.691
University	3454	22.3	0.96	0.84 to 1.09	0.507	3.0	0.96	0.74 to 1.23	0.730
Employment									
Employed	64,340	19.2	1.00	—	—	3.4	1.00	—	—
Unemployed	170,683	22.1	**1.09**	**1.04 to 1.14**	**<0.001**	3.0	0.99	0.94 to 1.05	0.764
Student	10,945	24.1	0.95	0.91 to 1.00	0.072	2.7	0.80	0.72 to 0.89	**<0.001**
Referral source									
VCT	121,865	18.4	1.00	—	—	3.0	1.00	—	—
PMTCT/EID	37,098	30.5	**1.24**	**1.15 to 1.34**	**<0.001**	1.2	**0.76**	**0.64 to 0.91**	**0.003**
TB clinic	7132	29.0	**1.11**	**1.00 to 1.23**	**0.043**	4.4	0.86	0.68 to 1.08	0.183
HC referral	121,034	22.6	**1.13**	**1.03 to 1.23**	**0.012**	3.6	1.11	0.97 to 1.27	0.137
Other	19,061	19.4	1.06	0.95 to 1.18	0.283	3.1	0.90	0.68 to 1.19	0.458
WHO stage									
I	76,685	23.1	1.00	—	—	1.5	1.00	—	—
II	52,260	18.8	0.98	0.93 to 1.03	0.490	2.0	**1.15**	**1.07 to 1.24**	**<0.001**
III	82,044	20.4	**1.12**	**1.05 to 1.18**	**<0.001**	3.5	**1.66**	**1.53 to 1.80**	**<0.001**
IV	21,372	26.3	**1.40**	**1.31 to 1.50**	**<0.001**	8.2	**3.13**	**2.86 to 3.43**	**<0.001**
Weight categories, kg									
<45	33,333	28.3	1.00	—	—	6.5	1.00	—	—
45–60	120,535	21.3	**0.79**	**0.76 to 0.81**	**<0.001**	3.0	**0.56**	**0.53 to 0.58**	**<0.001**
>60	52,667	17.8	**0.68**	**0.65 to 0.72**	**<0.001**	1.7	**0.37**	**0.34 to 0.40**	**<0.001**
CD4 count category									
<50	28,226	23.9	1.00	—	—	6.2	1.00	—	—
50–200	86,194	19.8	**0.90**	**0.88 to 0.93**	**<0.001**	3.1	**0.64**	**0.60 to 0.67**	**<0.001**
201–350	71,741	20.4	**0.85**	**0.82 to 0.88**	**<0.001**	1.9	**0.46**	**0.43 to 0.49**	**<0.001**

	Original	LTFU				Death			
	n	Rate/100PY	AHR	95% CI	*P*	Rate/100PY	AHR	95% CI	*P*
351–500	12,862	26.8	**0.93**	**0.89 to 0.97**	**0.002**	2.4	**0.48**	**0.43 to 0.53**	**<0.001**
>500	9660	32.0	0.99	0.92 to 1.06	0.755	2.7	**0.51**	**0.45 to 0.57**	**<0.001**
CASG patient *									
No	299,569	22.2	1.00	—	—	3.2	1.00	—	—
Yes	6766	2.7	**0.65**	**0.46 to 0.91**	**0.013**	0.4	1.05	0.82 to 1.35	0.697
Site size †									
1st quintile	5820	29.7	1.00	—	—	7.7	1.00	—	—
2nd quintile	18,384	27.2	1.02	0.86 to 1.20	0.841	4.8	**0.70**	**0.55 to 0.90**	**0.005**
3rd quintile	38,393	24.1	0.92	0.76 to 1.11	0.392	4.5	**0.65**	**0.50 to 0.84**	**0.001**
4th quintile	68,836	21.0	0.85	0.67 to 1.07	0.174	3.7	**0.56**	**0.41 to 0.76**	**<0.001**
5th quintile	174,902	20.2	0.84	0.64 to 1.11	0.217	2.4	**0.39**	**0.27 to 0.56**	**<0.001**
Back-bone									
Zidovudine	166,840	28.8	1.00	—	—	2.5	1.00	—	—
Stavudine	113,820	15.8	0.98	0.92 to 1.05	0.559	3.4	**1.48**	**1.36 to 1.62**	**<0.001**
Tenofovir	16,104	46.3	1.04	0.87 to 1.24	0.659	3.8	1.45	0.78 to 2.70	0.240
Other	2030	27.3	1.12	0.97 to 1.29	0.128	2.3	1.09	0.82 to 1.46	0.552
Third drug									
Nevirapine	248,958	20.2	1.00	—	—	2.9	1.00	—	—
Efavirenz	42,903	32.6	**1.09**	**1.04 to 1.15**	**0.001**	5.1	1.12	0.99 to 1.26	0.076
Protease inhibitor	4118	23.0	**1.29**	**1.11 to 1.50**	**0.001**	2.3	0.88	0.68 to 1.14	0.325
Other	2815	26.2	1.13	0.92 to 1.41	0.250	2.7	1.12	0.81 to 1.54	0.485

*A separate binary variable indicating presence or absence of a CASG program at the facility was included in the multivariable model in case facilities selected for CASG scale-up were different to other facilities, but this variable was not a statistically significant predictor of either death or LTFU.

†The categorical variable indicating rate of enrollment at the site, coded into quintiles as a 5-level variable, was included in the multivariable model but was not statistically significant predictor of either death or LTFU.

Values in bold indicate statistical significance at a level of $P \leq 0.05$.

HC, health center; PMTCT/EID, prevention of mother-to-child transmission/early infant diagnosis; PY, person-years; TB, tuberculosis; VCT, voluntary counseling and testing.