Published in final edited form as:

Pediatr Infect Dis J. 2015 August ; 34(8): e191–e199. doi:10.1097/INF.0000000000000741.

Temporal Trends in Patient Characteristics and Outcomes Among Children Enrolled in Mozambique's National Antiretroviral Therapy Program

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Abstract

Background: During 2004–2009, >12,000 children (<15 years old) initiated antiretroviral therapy (ART) in Mozambique. Nationally representative outcomes and temporal trends in outcomes were investigated.

Methods: Rates of death, loss to follow-up (LTFU), and attrition (death or LTFU) were evaluated in a nationally representative sample of1,054 children, who initiated ART during 2004–2009 at 25 facilities randomly selected using probability-proportional-to-size sampling.

Results: At ART initiation during 2004–2009, 50% were male, median age was 3.3 years, median CD4% was 13%, median CD4 count was 375 cells/μL, and median weight-for-age z-score was −2.1. During 2004–2009, median time from HIV diagnosis to care initiation declined from 33 to 0 days (p=0.001), median time from care to ART declined from 93 to 62 days (p=0.004), the percentage aged <2 at ART initiation increased from 16% to 48% (p=0.021), the percentage of patients with prior tuberculosis declined from 50% to 10% (p=0.009), and the percentage with

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Meetings: Presented In Part At The 5th Pediatric HIV Conference, Kuala Lumpur, Malaysia, June28–29, 2013.

Disclosures: The Authors Have No Conflicts Of Interest Or Funding To Disclose.

prior lymphocytic interstitial pneumonia declined from 16% to 1% (p<0.001). Over 2,652 person-years of ART, 183 children became LTFU and 26died. Twelve-month attrition was 11% overall, but increased from 3% to 22% during 2004–2009, due mainly to increases in 12-month LTFU (from 3% to 18%).

Conclusion: Declines in the prevalence of markers of advanced HIV diseaseat ART initiation probably reflect increasing ART access. However, 12-month LTFU increased during program expansion, and this negated any program improvements in outcomes that might have resulted from earlier ART initiation.

Keywords

Pediatric Antiretroviral Therapy; Treatment Outcomes; Mozambique

In Mozambique about 85 children acquireHIV daily through mother-to-child transmission.[1] Without treatment, available evidence from African clinical trials suggests that about half would die before their second birthday.[2] Despite global urgency to expand antiretroviral therapy (ART) access for children, progress has been sub-optimal in low- and middle-income countries.[3] In Mozambique, only about 27% of theestimated 100,000 ART-eligible children were receiving ART by 2013, compared with 48% of 590,000 ART-eligible adults.[4]

Expanding ART access for HIV-infected children is a priority of the Mozambican Ministry of Health (MOH) and partners, including the United States Government through its President's Emergency Plan for AIDS Relief. However, rapid expansion of a national ART program can result in decreasing care quality; for example in adult ART programs in South Africa[5] and Mozambique[6] rates of loss to follow-up (LTFU) increased during program expansion. In addition, a recent multi-country study of pediatric treatment outcomes reported increasing rates of LTFU among pediatric ART enrollees in certain African and South East Asian countries.[7] However, nationally representative trends in pediatric ART outcomeshave not yet been evaluated in Mozambique. As Mozambique considers adoption of new 2013 World Health Organization (WHO) guidelines, with expanded ART eligibility criteria, evaluating trends in mortality and LTFU is needed to inform future scale-up.

METHODS

ARTEligibility

During 2004–2009, HIV-infected children, aged 0–14 years, with World Health Organization (WHO) clinical stage III/IV were ART-eligible, regardless of $CD4^+$T-cell (CD4) count or percentage (%). In addition, during 2004–2008, children <18 months with CD4% <20%, and children ≥18 months with CD4%<15% were ART-eligible, while during 2009 children <36 months with CD4% <20%, and children ≥36 months with CD4%<15% were ART-eligible. Prescription of co-trimoxazole (CTX), was indicated for all pediatric ART patients until immune restoration.

Recommended first-line ART regimens includedeither stavudine (D4T) or zidovudine (AZT) with lamivudine (3TC) and either nevirapine (NVP) or efavirenz (EFV) depending on the child's age or weight. A regimen containing ritonavir-boosted lopinavir (LPV/r) was

recommended for children<2 with prior exposure to prevention of mother-to-child transmission (PMTCT) antiretrovirals.

Patient Monitoring

At baseline and every 6 months, weight measurements, staging, and CD4 counts and percentageswere recommended to monitor disease progression or improvement.[8] Alanine aminotransferase (ALT) measurements were recommended at baseline and every six monthsor for suspected liver disease. Patients or their caregivers collected medications monthly from the pharmacy according to MOH guidelines, or, in rare cases, every 2–3 months, if there was a valid reason for lengthier time periods between pharmacy appointments.

Study Design

This was a retrospective cohort study using routinely collected data abstracted from paper ART medical records of children initiating ART during 2004–2009.

Sample Size

To estimate 6-month attrition with a 95% confidence interval (CI) of±3%, conservatively expecting 6-month attrition of 25%,[9] and using a design effect of 1.5, a sample size of 1,130 charts was needed. We aimed to sample 1,500charts.

Sampling

During 2004–2009, 12,674 children (<15 years old) started ART at one of 210 facilities. To keep the study feasible, very small facilities (i.e., those with<20 pediatric ART enrollees) were excluded from the sample frame. Only 714 (6%) of all enrollees had enrolled at 93 very small facilities during 2004–2009. The remaining 117 study-eligible facilities were stratified by number of enrollees into three strata (1) ≥200, (2) 50–199, and (3) 20–49. Probability-proportional-to-size sampling was used to select five, 23, and seven facilities from strata one, two, and three, respectively. Simple random sampling was used to select 1,500 medical records from the 35 selected facilities, with 150 records selected from each facility in stratum one and 25 records from each facility in strata two and three.

Due to higher-than-expected costs of transport and data collection, only 25 of 35 randomly selected facilitiescould be included in the study, reducing the sample size to 1,250 medical records. In addition, 196of 1,250 charts could not be located at the 25 selected facilities. Therefore, only 1,054 medical records were abstracted between June 2010 and June 2011.

Treatment Outcomes

The primary outcomes of interest weremortality and LTFU.A childwas considered LTFU if he/she was absent from the facility in the 90days preceding data abstraction.[6] In rare cases, if it was clear a child's pharmacy pick-up appointments were scheduled at intervals of >90 days, and the child had not missed a future drug pick-up appointment, the child was considered alive on ART.

The combined outcome of attrition (death or LTFU) was a secondary outcome of interest. For all time-to-event analyses, transfers were censored at the date of transfer.

Exposure Variables

Most routinely collected variables on MOH-recommended ART records were abstracted (Table 1). Weight was recoded as weight-for-age z-score (WAZ), using Centers for Disease Control and Prevention (CDC) growth curves for children aged 5–14 years and WHO curves for children aged 0–<5 years. Severe immunodeficiency was defined using WHO-recommended age-specific thresholds.[10]

Analytic Methods

Data were analyzed using STATA 11 (StataCorp, 2009, Stata Statistical Software, Release 11, College Station, TX). Data were weighted and survey procedures used to account for study design.

Missing data are reported for each covariate of interest. The missing at random (MAR) assumption was considered plausible based on examination of patterns of missingness. If <30% of observations were missing data for a baseline demographic or clinical covariate of interest, multiple imputation with chained equations was used to impute the missing data.[11] The ice procedure in STATA was used to create 20 imputed datasets for each of three outcomes: LTFU, death, and attrition.[11] The imputation model included the event indicator, all study variables, and the Nelson-Aalen estimate of cumulative hazard.[12]

To assess the association between baseline characteristics and year of ART initiation, linear, logistic, ordered, or multinomial logistic regression models, accounting for study design, were used for continuous, binary, ordinal, and nominal categorical variables, respectively.

A competing risk model was used toanalyze the independent risk of the two failures types: death and LTFU. LTFU is acompeting cause of death, potentially increasing the risk of death because of ARTinterruption. Thus, assumptions about the independence of these two outcomes are notrealistic.[13] For this reason, we used a cumulative incidence function (CIF) to estimate thecumulative probability of each outcome during follow-up.

To estimate adjusted hazard ratios (AHRs) and 95% confidence intervals (CIs) for baseline covariates of interest, we usedCox proportional hazards regression models for each of the two competing outcomes (LTFU and mortality) and the combined outcome (attrition). Certainpatient-level covariates at ART initiation were considered *apriori* variables for inclusion in the multivariable models based on prior publications.[9] Prior reports from Mozambique suggest that quality of WHO staging was sub-optimal and so WHO stage was not an *apriori* risk factor.[14]

The proportional hazards assumption was assessed using visual methods and the Grambsch and Therneau test.[15] Estimates were combined across the imputed datasets according to Rubin's rules using the mim procedure in STATA.[16]

Ethics Approval

This study was approved by the MozambicanEthics Review Committee andthe Institutional Review Board (IRB) of the U.S. Centers for Disease Control and Prevention (CDC).

RESULTS

Trends in Demographic Characteristics

Among 1,054 childrenthe median age was 3.3 years, with33% <2 years old, 31% aged 2–<5, 28% 5–<10, and 9% aged 10–<15 (Table 1). During 2004–2009, the proportion of children aged <2 at ART initiation increased from 16% to 48% (p=0.021).

During 2004–2009, about 50% of children were maleand this percentage did not change significantly over time (Table 1). At ART initiation, 17% of children were maternal orphans and 19% paternal orphans. The proportion of children who were maternal orphans changed significantly over time from 10% during 2004to 29% in 2005, 25% in 2006, 18% during 2007–2008, and 9% in 2009 (p=0.001).

Referral source was a PMTCT clinic for 4% of children, but this proportion increased marginally from 1% to 6% during 2004–2009 (p=0.071) (Table 1). Referral source was an in-patient setting in 18% of children, but this decreased from 33% to 10% during 2004–2009 (p=0.001).

Median time from HIV diagnosis to entry into care was one day overall, but declined from 33 days in 2004 to 0 days in 2009 (p=0.001) (Table 1). Median time from HIV care initiation to ART initiation was 63 days but declined from 93 to 62 days during 2004–2009 (p=0.004). About half the children were enrolled at large clinics with >100 ART enrollees at the time of sampling (49%) and half at smaller clinics with 20–100 pediatric ART enrollees (51%) and this did not change significantly over time.

Trends in Clinical Characteristics

Overall, 15% of children had active TB at ART initiation, but there was a borderline statistically significant decline from 31% to 10% during 2004–2009 (p=0.093) (Table 2). Also, 14% of children had been diagnosed with and completed treatment for TB, before ART initiation, but this declined from 50% to 10% during 2004–2009 (p=0.009). Documentation of a diagnosis of pneumonia of unspecified cause before ART was found in 19% of all records, but declined from 65% to 14% during 2004–2009 (p=0.015). Documentation of a diagnosis oflymphocytic interstitial pneumonia (LIP) before ART was found in 4% of charts, but this declined from 16% to 1% during 2004–2009 (p<0.001). Documentation of a diagnosis of *Pneumocystisjirovecii* pneumonia (PCP) before ART was found in 2% of charts and this did not change over time.

The proportion of records documenting maternal antiretroviral prophylaxis or treatment was 17%, but this increased from 11% to 36% during 2004–2009 (p=0.009) (Table 2). The proportion of records documenting infant antiretroviral prophylaxis was 9%, but this increased from 4% to 17% during 2004–2009 (p=0.028).

Median WAZ was −2.1 and median weight-for-height z-score was −0.7 and these medians did not change significantly over time (Table 2). Median CD4% was 13% and median CD4 count was 375 cells/μL. At ART initiation during 2004–2009, median CD4% ranged from 10–13% and median CD4 count ranged from 204–307 cells/μL, but no statistically significant changes were noted. Median hemoglobin was 9.5 g/dL and this did not change over time. Severe immunodeficiency prevalence at ART initiation was 75% (95% CI, 70–81%), and this did not change significantly over time.

The proportion of children with ALT measurements within normal limits (ALT<56/μL) was 83% overall, but there was a marginally significant decline from 93% to 79% during 2004–2009 (p=0.098). Overall 42% of children were prescribed CTX at ART initiation and this did not change over time.

First-line Regimens

The most common ART regimens prescribed to children ≤3 years old were AZT, 3TC, and NVP (55%), and D4T, 3TC, and NVP (38%)(Table 3). D4T, 3TC, and NVP accounted for the majority of first-line regimens for children >3 years old (83%). Overall, 61% of children received D4T, 3TC, and NVP while 30% received AZT, 3TC, and NVP.Only 3 (<1%) of all children were prescribed LPV/r-containing regimens. Regimen distributions did not change significantly during 2004–2009 (p=0.478).

Mortality and LTFU

Over 2,652 person-years of follow-up, 209 children were lost through attrition;26were documented to have died, and 183became LTFU.

LTFU rates were 6.9/100 patient-years (PY) overall, but higher in days 0–90 (20.2/100 PY) compared with the time period following the first 90 days of ART (5.5/100 PY). Documented mortality rates were 0.98/100 PY overall, and were higher in days 0–90 (1.6/100 PY) compared with the time period following the first 90 days of ART (0.9/100 PY). Overall attrition rates were 7.9/100 PY but higher in days 0–90 (21.7/100 PY) compared with the time period following the first 90 days of ART (6.4/100 PY).

For all enrollees during 2004–2009, attritionproportions at 6, 12, 24, 36, 48, and 60 months were 7.4%, 11.0%, 16.6%, 20.2%, 24.2%, and 28.6%. However, attritionrates were higher for children enrolled in later calendar years compared with the 2004 and 2005 cohorts, increasing from 1.7/100 PY for 2004 and 2005 enrollees to 19.9/100 PY for 2009 ART enrollees. Similarly, 12-month attritionincreased from 3.0% for 2004 and 2005 ART enrollees to9.9%, 10.3%, 14.6%, and 21.6% for 2006, 2007, 2008, and 2009 ART enrollees, respectively (Table 4). Increases in 12-month attrition proportions during this time period were due to increases in documented 12-month mortality (from 0% to 4.0%) and LTFU (from 3.0% to 17.6%) (Table 4).

Predictors of Death and LTFU

Being one year older at ART initiation was marginally associated with lower risk of documented death (AHR 0.68; 95% CI, 0.46–1.00, p=0.051), but no reduction in LTFU rates

(Table 5). Initiating ART one calendar year later during program expansion was associated with nearly two-fold higher rates of LTFU (AHR 1.90; 95% CI, 1.31–2.77), but was not associated with mortality in either crude or multivariable analysis.

A one-unit higher WAZ at ART initiationwas associated with a 25% reduction in LTFU rates (AHR 0.75; 95% CI, 0.64–0.89). In unadjusted analysis, a one-unit increase in WAZ was associated with a 19% reduction in documented mortality, but in adjusted analysis this association was not significant.

A raised ALT level at ART initiation was associated with increased rates of LTFU (AHR 1.71; 95% CI, 1.02–2.89) but not documented mortality.

In multivariable analysis, later year of ART initiationwas predictive of attrition (AHR 1.80; 95% CI, 1.29–2.51), whereas a one-unit higher WAZat ART initiation was protective against attrition (AHR 0.77; 95% CI, 0.66–0.89)..

DISCUSSION

This is the first nationally representative evaluation of trends in pediatric ART outcomesfrom Mozambique. The key finding is that despite declines in the prevalence of markers of advanced HIV disease at ART initiation, increasing rates of LTFU have negated any potential improvements in program outcomes that might have resulted from earlier ART initiation.

Trends in ART Enrollment Characteristics

During 2004–2009, the proportion of children starting ART aged <2 years old increased from 16% to 48%. In addition, during 2004–2009, prevalence of various markers of advanced HIV disease at ART enrollment declined.

This trend of initiating ART at younger agesand earlier disease stages is probably due to increasing access to HIV testing services, earlier enrollment in HIV care, and the change in national guidelines in January 2009 that recommended ART initiation at earlier disease stages. The trend of earlier ART initiation is encouraging for program managerssince earlierART for peri-natallyHIV-infected childrenis associated with improved survival.[17] In accordance with WHO recommendations,[18] in December 2009, ART was recommended for all infants, and in December 2010, all children aged <2 years old became ART-eligible in Mozambique. These changes could further lower both the median age of ART initiation and the prevalence of markers of advanced HIV disease.

ART prescribing practices did not change over time. About91% of children >3 years old were prescribed NVP-containing regimens, while the other 9% were prescribed EFV-containing regimens. Clinician preference for NVP over EFV may be related to cost differences and possibly clinician concerns about teratogenicity among the relatively few female adolescents who were sexually active.[19] However, recent data suggests EFV-containing regimens may be superior to NVP-containing regimens in achieving virologic suppression, which might influence guidelines and prescribing practices.[19]

During 2006–2009, LPV/r-containing regimens were recommended for children <2 years old at ART initiation, who were PMTCT antiretroviral exposed, to reduce risk of virologic failure.[20] Limited LPV/r use may have been due to cost or lack of cold-chains for LPV/r formulations. As more children start ART at age <2 years, using currently available LPV/r formulations, wherever the cold chain allows, will be important. In addition, development of heat-stable LPV/r-containing regimens suitable for young children is necessary[21] and may soon be commercially available.[22]

Trends in Outcomes

Our overall reported 12-month attrition (11.0%) is similar to other reports [0–20% according to a recent meta-analysis].[9] However, the increase in 12-month attrition from 3.0% to 21.6% during 2004–2009, due mainly to increases in observed LTFU (from 3.0% to 17.6%) is concerning. Increasing rates of LTFU have been observed in adult African ART programs[5,6] and in a recent multi-country analysis among pediatric ART enrollees.[7] However, most previous reports of trends in pediatric ART retention[23,24] showed no significant changes in LTFU over time. Possible explanations for increasing LTFU in Mozambiqueinclude: (1) increasingrates of undocumented transfer of patients between health facilities, (2) declines in record keeping quality, and (3) overcrowded facilities.

In Mozambique, two initiatives combined to increase the rate of transferal of HIV-infected ART enrollees between health facilities: (1) as large central facilities became overloaded, down-referral of ART enrollees to primary health care clinics (PHCs) was encouraged during 2004–2009,[25] and (2) in March 2008, the MOH, in an effort to reduce HIV stigma, decided to close 23 day hospitals that provided HIV care and treatment services exclusively to HIV-infected patients, and relocated the patients to general health services.[26] During these initiatives, common problems included poor transfer documentation, which could have resulted in “silent transfers” being observed as LTFU, and lack of tracing for defaulting patients.[25]

Secondly, with increasing patient load, attention to timely, accurate maintenance of medical records may have been compromised, resulting in the possibility of missing entries for the most recent clinic visit.[5] Implementing effective electronic monitoring systems with dedicated personnel to manage these systems could improve data quality.[27]

Thirdly, Mozambique has a severe healthcare worker shortage, with only 0.04 doctors and 0.21 nurses per 1,000 inhabitants,[28] and with increasing patient-to-provider ratios, patient waiting times have increased, and waiting rooms have become more crowded.[25] This may be associated with patient and clinician dissatisfaction with clinic conditions, which might have caused increasing LTFU.[29] In addition, Mozambique is ranked 185th out of 187 countries on the United Nations Human Development Index, and for many patients in more rural areas enrolled in later program years, transport to and from ART clinic visits, may have become increasingly economically infeasible.[30] Possible strategies to reduce burdens on health facilities and patients include formation of community ART groups[31] or distribution of ART at community locations.[32]

Other Predictors of Outcomes

Similar to other reports,[33] ART enrollment at younger ages was borderline predictive of increased mortality risk. This probably reflects the difficulties treating younger children with ART, including more rapid disease progression, limited repertoire of antiretroviral formulations, unpalatable liquid formulations, and adherence challenges.[3] In Mozambique, earlier ART enrollment through expansion of early infant diagnosis and treatment services, and provision of optimal ART regimens (e.g. LPV/r for PMTCT-exposed infants) could improve young child outcomes.

As in other studies,[9] moderate or severe under-nutrition (WAZ≤−2) was common at ART initiation, and having a lower WAZ score at ART initiation was predictive of poor outcomes. HIV-associated under-nutrition has multiple causes, including poor intake, poor absorption, increased basal metabolic requirements, and co-existing opportunistic infections.[34] Food insecuritymay be an important factor in Mozambique given the high prevalence of poverty. Undiagnosed tuberculosis may also be a common cause of under-nutrition in Mozambique. [35] Scale-up of the WHO-recommended HIV nutrition program,[36] and regular TB screening in conjunction with use of the newXpert MTB/RIF assay for TB diagnosis,[37] could help to improve ART outcomes for undernourished children.

In this study, prevalence of raised ALT (>56 U/L)increased marginally among ART enrollees over time and a raised ALT was independently associated with LTFU risk. Other studies have reported that up to 20% of pediatric ART enrollees have some evidence of liver dysfunction.[38] There are many possible causes for raised ALT in HIV-infected children,[39] including viral co-infections (e.g. Hepatitis B)and drug-related liver toxicity, [e.g. secondary to sulphonamides, anti-TB treatment,[38] or PMTCT antiretrovirals].[40] Chronic Hepatitis B infection, thought to affect about 5–10% of HIV-infected children in Africa,[41] is a possible explanation for increased ALT levels. Regardless of the cause of increased ALT levels, this was significantly associated with LTFU, increasing the importance of the observed trend for program managers and further research.

Limitations

This report is subject to at least sixlimitations. Firstly, this was a retrospective cohort study utilizing routinely collected data. Secondly, missing data on patient characteristics at ART start likely introduced non-differential measurement error. Thirdly, ten of 35 ART delivery sites could not be evaluated due to financial and logistical constraints, and this may have introduced selection bias, reducing ability to generalize findings to all facilities in the country. Fourthly, mortality may be underestimated and LTFU overestimated, due to lack of active tracing.[42] Fifthly, these data represent trends among children starting ART during 2004–2009 only, and do not represent more recent trends. Finally, viral load was not routinely monitored and so virologic outcomes were not captured.

CONCLUSIONS

Declines in median age and prevalence of markers of advanced HIV disease at ART initiationare encouraging for program managers as they likely indicate increasing access to

HIV care and treatment services; however, despite gains in ART access, ART program outcomes have worsened over time due to increasing rates of LTFU. Causes of increasing rates of LTFU are unknown but could relate to poor documentation of increasing inter-facility transfers, sub-optimal record-keeping, or patient/caregiver frustration with overcrowded facilities.

Sources Of Support:

This Research Has Been Supported By The President's Emergency Plan For AIDS Relief (PEPFAR) Through The U.S. Centers For Disease Control And Prevention.

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Table 1:

Demographic Characteristics among Children Starting Antiretroviral Therapy in Mozambique during 2004–2009

	Original (N=1,054)*			Imputed							
	n	Median or %**	(IQR or 95% CI)	Median or %**	(IQR or 95% CI)	2004 (n=18, 2%)	2005 (n=62, 5%)	2006 (n=162, 15%)	2007 (n=326, 29%)	2008 (n=289, 27%)	2009 (n=197, 19%)	P-value
Age (Median)												
Both Sexes	1,054	3.3	(1.7–6.5)	3.3	(1.7–6.5)	4.7	4.5	3.5	3.1	3.4	2.1	**0.065**
Age Categories												
0-<2 years	327	33%	(28–37%)	33%	(28–37%)	16%	12%	22%	31%	33%	48%	**0.021**
2-<5 years	330	30%	(27–34%)	31%	(27–34%)	49%	43%	38%	33%	27%	21%	
5 to <10 years	301	28%	(24–32%)	28%	(24–32%)	23%	28%	35%	28%	30%	20%	
10 to <15 years	96	9%	(7–11%)	9%	(7–11%)	12%	16%	6%	9%	9%	11%	
Sex												
Male	523	50%	(46–53%)	50%	(46–53%)	46%	46%	51%	53%	44%	54%	0.597
Female	531	50%	(47–54%)	50%	(47–54%)	54%	54%	49%	47%	56%	46%	
Maternal Vital Status												
Mother deceased at ART start	173	17%	(13–21%)	17%	(13–21 %)	10%	29%	25%	18%	18%	9%	**0.001**
Observations missing data	62	6%										
Paternal Vital Status												
Father deceased at ART start	173	19%	(15–22%)	19%	(16–23 %)	10%	20%	19%	22%	18%	18%	0.848
Observations missing data	129	12%										
Dual Orphan Status												
Both parents deceased	51	6%	(4–8%)	6%	(4–8%)	0%	8%	8%	7%	6%	2%	0.167
Observations missing data	218	21%										
Referral Source (recoded)												
General Health Facility (outpatient)	332	34%	(23–46%)	34%	(22–46%)	46%	31%	34%	28%	32%	45%	
TB clinic	9	1%	(0–2%)	1%	(0–3%)	0%	1%	0%	1%	2%	1%	0.641

	Original (N=1,054)*			Imputed								
	n	Median or %**	(IQR or 95% CI)	Median or %**	(IQR or 95% CI)	2004 (n=18, 2%)	2005 (n=62, 5%)	2006 (n=162, 15%)	2007 (n=326, 29%)	2008 (n=289, 27%)	2009 (n=197, 19%)	P-value
PMTCT clinic	28	4%	(1–6%)	4%	(1–6%)	1%	0%	1%	3%	6%	6%	**0.071**
VCT	334	36%	(20–53%)	36%	(20–53%)	15%	35%	38%	40%	40%	29%	0.460
Inpatient referral	224	18%	(11–25%)	18%	(11–25%)	33%	28%	25%	21%	16%	10%	**0.001**
Other	62	6%	(3–9%)	6%	(3–9%)	5%	5%	3%	8%	5%	9%	0.583
Observations missing data	65	6%										
Time from Diagnosis to Entry into HIV Care (days)§												
Both Sexes	785	1	(0–21)	1	(0–21)	33	18	2	2	1	-	**0.001***
Observations Missing Data	269	26%										
Time from HIV Care Start to ART Start (days)§												
Both Sexes	948	63	(28–183)	63	(29–184)	93	163	83	60	55	62	**0.004***
Observations Missing Data	106	10%										
Site type												
Large (>100 enrollees)	662	49%	(47–51%)	49%	(47–51%)	39%	70%	56%	54%	49%	33%	0.202
Small (≤100)	392	51%	(49–53%)	51%	(49–53%)	61%	30%	44%	46%	51%	67%	

Abbreviations: IQR, interquartile range; CI, confidence interval; TB, tuberculosis; PMTCT, prevention of mother-to-child transmission; VCT, voluntary counseling and testing center.

*The denominator used to estimate percentages presented in the original data columns was 1,054 minus the number of observations missing data.

**All percentages and medians presented in this table are weighted to account for survey design.

§The days-to-care and days-to-ART variables were log-transformed to approximate a normal distribution, and quadratic terms for year of ART initiation were included in the linear regression models since p-values for the quadratic and unmodified ART year coefficients were <0.05 and their signs opposite.

Table 2:

Clinical Characteristics of Children Starting Antiretroviral Therapy in Mozambique during 2004–2009

	Original*			Imputed								
	n	Median/%**	(IQR/95% CI)	Median or %**	(IQR/95% CI)	2004 (n=18, 2%)	2005 (n=62, 5%)	2006 (n=162, 15%)	2007 (n=326, 29%)	2008 (n=289, 27%)	2009* (n=197, 19%)	P-value
TB treatment at ART start												
Yes	163	15%	(7–22%)	15%	(7–22%)	31%	25%	15%	16%	13%	10%	**0.093**
No	887	85%	(78–93%)	85%	(78–93%)	69%	75%	85%	84%	87%	90%	
Observations Missing Data	4	0%										
Prior TB												
Yes	156	14%	(9–20%)	14%	(9–20%)	50%	22%	14%	16%	12%	10%	**0.009**
No	894	86%	(80–91%)	86%	(80–91%)	50%	78%	86%	84%	88%	90%	
Observations missing data	4	0%										
Prior Pneumonia												
Yes	221	19%	(12–26%)	19%	(12–26%)	65%	24%	19%	22%	15%	14%	**0.015**
No	829	81%	(74–88%)	81%	(74–88%)	35%	76%	81%	78%	85%	86%	
Observations missing data	4	0%										
Prior PCP												
Yes	16	1%	(1–2%)	2%	(1–2%)	5%	3%	2%	2%	2%	1%	0.252
No	1034	99%	(98–99%)	98%	(98–99%)	95%	97%	98%	98%	98%	99%	
Observations missing data	4	0%										
Prior Lymphocytic Interstitial Pneumonia												
Yes	48	4%	(0–8%)	4%	(0–8%)	16%	13%	9%	3%	2%	1%	**<0.001**
No	1002	96%	(92–100%)	96%	(92–100%)	84%	87%	91%	97%	98%	99%	
Observations missing data	4	0%										
Maternal ARVs Received During Pregnancy/Delivery												
Yes	83	13%	(10–16%)	17%	(12–22%)	11%	6%	9%	13%	14%	36%	**0.009**
No	613	87%	(84–90%)	83%	(78–88%)	89%	94%	91%	87%	86%	64%	

	Original*			Imputed								
	n	Median/%**	(IQR/95% CI)	Median or %**	(IQR/95% CI)	2004 (n=18, 2%)	2005 (n=62, 5%)	2006 (n=162, 15%)	2007 (n=326, 29%)	2008 (n=289, 27%)	2009* (n=197, 19%)	P-value
Observations missing data	358	34%										
Infant exposure to PMTCT ARVs after birth												
Yes	35	5%	(3–8%)	9%	(5–14%)	4%	2%	4%	7%	9%	17%	**0.028**
No	696	95%	(92–98%)	91%	(86–95%)	96%	98%	96%	93%	91%	83%	
Missing	323	31%										
Weight-for-Age Z-score (Median)												
Both Sexes	888	−2.1	(−3.3– −1.1)	−2.1	(−3.3– −1.1)	−1.8	−1.8	−2.4	−2.3	−2.1	−1.8	0.594
Observations missing data	166	16%										
Weight-for-Height Z-score (Median)												
Both Sexes	635	−0.7	(−2– 0.4)	−0.7	(−2.1– 0.5)	0.4	0.04	−0.5	−0.9	−0.7	−0.9	0.347
Observations missing data	419	40%										
CD4 cell % (Median)												
All ages	766	12.6	(7.9–17.9)	13	(8–18)	10	13	12	13	13	13	0.935
Observations missing data	288	27%										
CD4 cell count (Median)												
All ages	791	382	(111–652)	375	(97–652)	204	406	380	400	396	307	0.871
Observations missing data	263	25%										
Hemoglobin												
All ages	798	9.5	(8.5–10.4)	9.5	(8.4–10.5)	9.9	9.9	9.6	9.6	9.4	9.5	0.248
Observations missing data	256	24.3										
Alanine Aminotransferase Categories (ALT)												
Normal (≤56/uL)	618	88%	(84–91%)	83%	(78–88%)	93%	91%	88%	87%	77%	79%	**0.098**
Moderately abnormal (57–100/uL)	32	5%	(3–8%)	9%	(6–13%)	5%	7%	7%	7%	12%	11%	
Abnormal (>100/uL)	43	7%	(4–10%)	8%	(5–11%)	2%	2%	6%	6%	12%	9%	

Pediatr Infect Dis J. Author manuscript; available in PMC 2020 August 17.

	Original*			Imputed							
	n	Median/%**	(IQR/95% CI)	Median or %**	(IQR/95% CI)	2004 (n=18, 2%)	2005 (n=62, 5%)	2006 (n=162, 15%)	2007 (n=326, 29%)	2008 (n=289, 27%)	2009* (n=197, 19%)	P-value
Observations missing data	361	34%										
CTX prescription												
Yes	305	48%	(28–68%)	42%	(29–56%)	54%	42%	41%	46%	38%	42%	0.684
No	345	52%	(32–72%)	58%	(44–71%)	46%	58%	59%	54%	62%	58%	
observations missing data	404	38%										

Abbreviations: IQR, inter-quartile range; CI, confidence interval; TB, tuberculosis; PMTCT, prevention of mother-to-child transmission; ARVs, antiretrovirals; CTX, co-trimoxazole; PCP, *Pneumocystis jirovecii* pneumonia; ART, antiretroviral therapy

*The denominator used to estimate percentages presented in the original data columns was 1,054 minus the number of observations missing data.

**All proportions and medians presented in this table are weighted to account for survey design.

Table 3:

First-Line Antiretroviral Therapy Regimens Prescribed to HIV-infected Children in Mozambique during 2004–2009

	≤ 3 years old				> 3 years old				Overall			
	n	N	%	95% CI	n	N	%	95% CI	n	N	%	95% CI
D4T-3TC-NVP	148	450	38%	(27–49%)	423	514	83%	(76–89%)	571	964	61%	(55–68%)
D4T-3TC-EFV	6	450	1%	(0–2%)	35	514	7%	(3–11%)	41	964	4%	(2–6%)
D4T-3TC-LPV/r	3	450	0%	(0–1%)	0	514	0%	(0–0%)	3	964	0%	(0–1%)
AZT-3TC-ABC	20	450	4%	(2–7%)	2	514	0%	(0–1%)	22	964	2%	(1–3%)
AZT-3TC-NVP	268	450	55%	(44–66%)	40	514	8%	(4–11%)	308	964	30%	(24–37%)
AZT-3TC-EFV	1	450	0%	(0–1%)	10	514	2%	(0–4%)	11	964	1%	(0–2%)
D4T-3TC-ABC	2	450	0%	(0–1%)	4	514	1%	(0–1%)	6	964	1%	(0–1%)
D4T-3TC-other	1	450	0%	(0–1%)	0	514	0%	(0–0%)	1	964	0%	(0–0%)
D4T-AZT-NVP	1	450	0%	(0–1%)	0	514	0%	(0–0%)	1	964	0%	(0–0%)
missing	45	495	9%		45	559	8%		90	1054	9%	

Abbreviations: CI, confidence interval; D4T, stavudine; AZT, zidovudine; 3TC, lamivudine; NVP, nevirapine; EFV, efavirenz; ABC, abacavir; LPV/r, lopinavir-ritonavir.

Table 4:

Cumulative Incidence of Death andLTFUamong Children Initiating Antiretroviral Therapy in Mozambiqueduring 2004–2009

	Years on ART	2004–5	2006	2007	2008	2009
Death	**0.5**	0.0%	1.0%	0.8%	0.9%	1.9%
	1	0.0%	1.4%	1.3%	1.4%	4.0%
	2	0.0%	3.3%	3.5%	1.7%	4.0%
	3	0.0%	4.4%	3.8%	1.7%	4.0%
	4	3.6%	4.4%	3.8%	1.7%	4.0%
LTFU	**0.5**	3.0%	7.0%	5.9%	9.1%	12.4%
	1	3.0%	8.5%	9.0%	13.2%	17.6%
	2	3.0%	10.3%	13.5%	19.4%	32.1%
	3	3.0%	11.7%	18.4%	25.1%	32.1%
	4	4.8%	14.6%	26.2%	25.1%	32.1%
Attrition *	**0.5**	3.0%	8.0%	6.8%	10.0%	14.4%
	1	3.0%	9.9%	10.3%	14.6%	21.6%
	2	3.0%	13.6%	17.0%	21.1%	36.1%
	3	3.0%	16.1%	22.2%	26.7%	36.1%
	4	8.4%	19.0%	30.0%	26.7%	36.1%
Retention *	**0.5**	97.0%	92.0%	93.2%	90.0%	85.6%
	1	97.0%	90.1%	89.7%	85.4%	78.4%
	2	97.0%	86.4%	83.0%	78.9%	63.9%
	3	97.0%	83.9%	77.8%	73.3%	63.9%
	4	91.6%	81.0%	70.0%	73.3%	63.9%

Abbreviations: LTFU, lost to follow-up.

* Attrition is the cumulative incidence of death and LTFU, with transfer outs censored at the time of transfer. Retention is the proportion of children alive and on ART at the relevant time point (1-attrition).

Table 5:

Risk Factors for Death and LTFU among Children Starting Antiretroviral Therapy in Mozambique during 2004–2009

	Original		LTFU						Death						
	N	Rate/100	HR	Crude (95% CI)	p	AHR	Adjusted (95% CI)	p	Rate/100	Crude HR	(95% CI)	p	AHR	(95% CI)	p
Age															
Per year increase	1,054	—	**0.93**	**(0.87–1.00)**	**0.047**	0.95	(0.85–1.06)	0.308	—	0.87	(0.64–1.18)	0.360	**0.68**	**(0.46–1.00)**	**0.051**
Sex															
Male	523	8.77	1.00	—	—	1.00	—	—	1.53	1.00	—	—	1.00	—	—
Female	531	8.18	0.94	(0.70–1.27)	0.692	1.50	(0.96–2.32)	0.070	1.13	0.74	(0.23–2.35)	0.595	2.87	(0.47–17.48)	0.232
Maternal Vital Status															
Mother alive	819	8.63	1.00	—	—	1.00	—	—	1.46	1.00	—	—	1.00	—	—
Mother dead	173	7.85	0.96	(0.65–1.42)	0.826	1.64	(0.89–3.01)	0.105	0.80	0.58	(0.22–1.54)	0.255	1.33	(0.13–13.35)	0.791
ART Initiation year															
Per year increase	1,054	—	**1.57**	**(1.19–2.07)**	**0.003**	**1.90**	**(1.31–2.77)**	**0.002**	—	1.18	(0.75–1.87)	0.462	1.17	(0.70–1.95)	0.523
TB treatment															
No	887	9.03	1.00	—	—	1.00	—	—	1.32	1.00	—	—	1.00	—	—
Yes	163	5.76	0.67	(0.34–1.31)	0.224	0.90	(0.27–2.97)	0.849	1.33	1.04	(0.31–3.50)	0.948	0.41	(0.05–3.12)	0.360
Prior TB treatment															
No	894	9.12	1.00	—	—	1.00	—	—	1.26	1.00	—	—	1.00	—	—
Yes	156	5.23	**0.61**	**(0.38–0.96)**	**0.035**	1.03	(0.45–2.40)	0.933	1.62	1.35	(0.39–4.71)	0.620	3.49	(0.40–30.69)	0.237
Weight-for-Age Z-score															
Per unit increase	888	—	**0.82**	**(0.75–0.91)**	**0.001**	**0.75**	**(0.64–0.89)**	**0.004**	—	**0.81**	**(0.71–0.92)**	**0.004**	0.81	(0.52–1.25)	0.287
CD4 cell count %															
>20%	125	10.20	1.00	—	—	1.00	—	—	2.17	1.00	—	—	1.00	—	—
10–20%	389	8.96	0.89	(0.52–1.51)	0.643	1.31	(0.60–2.87)	0.435	1.00	0.45	(0.10–1.99)	0.269	0.47	(0.04–5.79)	0.524
<10%	252	6.93	0.70	(0.38–1.30)	0.238	1.07	(0.39–2.88)	0.884	1.36	0.64	(0.16–2.55)	0.500	2.01	(0.12–32.71)	0.595
Hemoglobin															
>=8g/dL	798	7.71	1.00	—	—	1.00	—	—	1.09	1.00	—	—	1.00	—	—
<8g/dL	256	13.03	1.61	(0.93–2.79)	0.082	1.39	(0.72–2.67)	0.293	2.74	2.41	(0.76–7.65)	0.126	1.66	(0.10–27.29)	0.699
ALT Categories															
Normal (≤56/uL)	618	6.19	1.00	—	—	1.00	—	—	0.84	1.00	—	—	1.00	—	—

	Original		LTFU						Death						
	N	Rate/100	HR	Crude (95% CI)	p	AHR	Adjusted (95% CI)	p	Rate/100	Crude HR	(95% CI)	p	AHR	(95% CI)	p
Abnormal (>56/uL)	32	13.32	**2.04**	**(1.23–3.37)**	**0.009**	**1.71**	**(1.02–2.89)**	**0.044**	0.87	0.91	(0.11–7.90)	0.930	0.85	(0.12–6.04)	0.859
CTX prescription															
Yes	305	7.93	1.00	—	—	1.00	—	—	1.44	1.00	—	—	1.00	—	—
No	345	8.91	1.08	(0.56–2.09)	0.810	1.56	(0.63–3.90)	0.301	1.23	0.82	(0.18–3.62)	0.774	0.77	(0.14–4.21)	0.728
Site type															
Large Central (>100)	662	5.74	1.00	—	—	1.00	—	—	0.44	1.00	—	—	1.00	—	—
Small-Medium (<=100)	392	12.33	1.95	(0.84–4.56)	0.116	1.85	(0.78–4.41)	0.150	2.57	5.32	(0.53–53.19)	0.146	6.46	(0.62–67.68)	0.111

Abbreviations: HR, hazard ratio; AHR, adjusted hazard ratio; ART, antiretroviral therapy; TB, tuberculosis; ALT, alanine aminotransferase; CTX, co-trimoxazole