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Paediatric access and continuity of HIV care before the start of antiretroviral therapy in sub-Saharan Africa

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Introduction

At the end of 2012, 630 000 children were receiving ART in low- and middle-income countries [1] and treatment outcomes were comparable or better than those reported among children treated in high-income countries [2]. However, researchers have highlighted the necessity to describe the cascade of patients enrolled in HIV care before the start of ART to appropriately assess the overall performance of HIV programmes [3]. Several studies have reported rates of programme attrition among HIV-infected children in Sub-Saharan Africa [4-10]. Descriptions of characteristics of paediatric patients at programme enrolment and of the dynamics of dropping out before the start of ART are nevertheless scarce. In Médecins Sans Frontières (MSF)-supported HIV programmes between 5% and 51% of children currently followed have not yet started ART (unpublished internal reports). We previously reported a high dropout rate of adult patients before the start of therapy, especially early after programme enrolment [11]. We have now conducted a longitudinal study to describe the cascade of care, characteristics, outcomes and associated risk factors of patients aged 5 to 14 years before the start of ART.

Methods

Study design and population

We analysed electronic medical records from HIV-positive patients aged 5-14 years, and treated in the four HIV programmes supported by MSF-France in Sub-Saharan Africa (two in

Kenya, one in an urban slum and one in a rural district hospital; one highly decentralized in a rural district of Malawi; and one in a rural hospital district of Uganda). Patient clinical and laboratory data were collected prospectively in each programme using the FUCHIA software (Follow-Up and Care of HIV Infection and AIDS, Epicentre, Paris). Patients enrolled in HIV care between January 2004 and December 2010 were eligible for inclusion. The databases censoring date was 31 December 2011.

Patients were clinically evaluated at enrolment and every 3 to 6 months, depending on the level of immunosuppression. National guidelines for patient management were followed and encompassed clinical staging and nutritional status monitoring, as recommended by the World Health Organization (WHO). At programme entry CD4 cell count testing was used to assess ART eligibility in patients with WHO clinical stage 1 or 2, and then every 6 months (3 months for patients with counts <500 cells/µL). No routine viral load (VL) monitoring or contact tracing were done. Eligibility criteria for ART start evolved over time, following changes in WHO recommendations.

Statistical analysis

Patient study follow-up started at the date of programme inclusion and ended at the earliest of the following events: death, transfer-out, ART initiation, or date of last clinic visit. Loss to follow-up (LFU) was defined as missing an appointment for more than 6 months at the database censoring date, in patients not transferred outside the programme or reported as dead [12].

Patient characteristics at HIV care enrolment were described using frequency and percentages for categorical variables and median and interquartile range (IQR) for continuous variables. Comparisons were made using Chi 2, and Wilcoxon or Kruskal-Wallis tests, respectively. For baseline clinico-immunological covariates, the closest record within 3 months of enrolment was used. A low BMI was defined as a BMI <18.5 kg/m^2 [13].

Access to HIV care was assessed through calculation of the time between HIV testing and enrolment in the programme. We examined temporal changes in the proportions of patients with a recorded CD4 cell count measurement within 1 and 3 months of enrolment. We also described temporal interruptions of care during follow-up (not attending a clinic visit for at least 60 days after the appointment date). The delay in ART start was estimated within the group of patients who were eligible for ART start at enrolment (patients with CD4 cell count <350 cells/µL and/or in WHO clinical stage 3 or 4) and initiated therapy.

Kaplan-Meier estimates of mortality, LFU and attrition (composite endpoint of death and LFU) were calculated within two time periods, 0-6 and 6-60 months after programme entry. Risk factors for these three outcomes were evaluated using parametric survival models with the Weibull distribution for the 0-6 month period, and Cox proportional-hazards models for the 6-60 month period. The following factors were considered for adjustment: gender, age, mode of entry in the programme, year of inclusion, WHO clinical stage, CD4 cell count, body mass index, and recorded diagnosis of tuberculosis. Final multivariate models were fitted using a backward stepwise approach. Statistical significance was assessed with the likelihood ratio test at the 5% level. All estimates were adjusted for year of programme inclusion and site. In sensitivity analyses only patients with complete covariate data were included in the

models. Mortality estimates were adjusted for lost to follow-up with a competing risk analysis and sub-hazard ratios (SHR) were obtained.[14]

Analyses were performed using Stata 12.1 software (Stata Corporation, College Station, Texas, USA).

Ethical review

All MSF-supported projects are implemented in collaboration with the Ministry of Health (MoH) and within the frame of signed Memorandums of understandings. Electronic monitoring data are collected in agreement with the MoH. The study was approved by the Comité de Protection des Personnes de St Germain en Laye, Paris, France.

Results

A total of 2,244 children were included in the analysis (Figure 1), 52.7% received care in Malawi, 21.2% in Uganda and 26.1% in Kenya. Number of inclusions remained stable over time (about 320 patients per year). The median duration from a positive HIV test result to care enrolment was 2 days [IQR 0-8].

Patient characteristics at care enrolment

Median age was 8.0 years [IQR 6.0-11.0] and was constant over time, 52.8% of patients were girls, 47% had a low BMI, 43% were in stage 3 or 4 and 9.9% had tuberculosis (Table 1). Baseline median CD4 count was 409 cells/µL [IQR 203-478] (n=1,654). The proportions of children with CD4 measurements within 1 and 3 months were 55.7% and 73.7%,

respectively. These proportions increased from 6.3% and 33.3% in 2004, to 80.4% and 88.5% in 2010, respectively. Three patients had history of PMTCT or ART use (0.1%).

Study follow-up and interruption of HIV care

Median duration of follow-up was 4.4 months [IQR 1.3-20].

During follow-up, 260 of the 2,244 patients included (11.6%) discontinued HIV care for a median of 90 days [IQR 70-153] and 78.0% of these interruptions happened after 6 months of follow-up. The proportion of patients who interrupted care was unrelated to mortality (p=0.060) and LFU (p=0.502).

ART eligibility and therapy start

During the study period, the percentage of patients with eligibility status known at enrolment increased from 74.0% in 2004 to 93.5% in 2010 (p<0.001). Among these patients, the proportion of children initially eligible for ART decreased from 95% in 2004 to 49.3% in 2010. The pre-ART cascade of care is displayed in Figure 1. ART eligibility at enrolment could be determined for 1,736 (77.4%) patients. Among them, 1,233 (71.0%) patients required therapy and 940 (76.3%) of these ART eligible children were initiated on ART after a median of 1.8 months [IQR 0.9–4.6]. Of those not eligible for ART and with unknown eligibility status at enrolment (n=1,011), 419 received ART in median 8.4 months [IQR 3.2–22.4] after enrolment

Mortality

A total of 68 (3.0%) children died before receiving ART in median 2.1 months [IQR 0.5–11.6] after programme entry, and 42 (61.8%) of them were eligible for ART (Figure 1). Mortality rate was 2.7/100 person-years (95%CI 2.1-3.4). Kaplan-Meier estimates were 1.3% (95% CI 0.9–1.9%), 2.5% (95% CI 1.8–3.4%), 3.5% (95% CI 2.6–4.6%) and 4.7% (95% CI 3.6–6.2%) at 1, 6, 12 and 24 months respectively. Mortality rates were 16.2/100 person-years at 1 month, 9.00/100person-years at 3 months, 3.0/100 person-years for the 1–6 month period, 2.0/100 person-years for the 6–12 month period and 1.3/100 person-years for the 12–24 month period. They were higher in patients eligible for ART than in those not eligible (5.2/100 vs. 0.7/100 person-years; Figure 2A).

During the first six months of follow-up, mortality was higher in patients with advanced clinical disease (adjusted hazard ratio [aHR]= 3.75, 95%CI 1.49–9.48 for stage 3 or 4 compared to stage 1 or 2) and lower in those with BMI ≥18.5 kg/m^2 (aHR=0.44 95%CI 0.22–0.87; Table 2). During the 6-60 month period, the highest aHR was observed for patients with tuberculosis (aHR=6.4, 95%CI 1.78-22.96). Mortality was lower in patients with BMI ≥18.5kg/m^2 (aHR=0.39, 95%CI 0.17-0.90), in those with CD4≥200 (aHR=0.05, 95%CI 0.01-0.41) and in those referred from the in/out patient department compared to those referred by VCT/PMTCT personnel (aHR=0.12, 95%CI 0.03-0.42). Results from the competing risk analysis were consistent.

Patients eligible for ART at enrolment had increased risk of mortality (aHR=14.55, 95%CI 1.94-108.76) during the first 6 months of follow-up compared to those not eligible. Estimate for the 6-60 month period was no longer significant (aHR=1.45 (95%CI 0.47-4.51).

Lost to follow-up

A total of 397 (17.7%) children were LFU in median 2.9 months [IQR 0.2–12.7] after programme entry. One hundred seventy-three (43.6%) of them were initially eligible for ART, 73 (18.4%) were not and 151 (38.0%) had unknown eligibility status (Figure 1). Twenty-five percent of patients who were eligible and LFU before ART start did not return after their enrolment visit. Overall LFU rate was 16.1/100 person-years. Kaplan-Meier estimates of LFU were 7.1% (95% CI 6.1–8.3%), 14.0% (95% CI 12.4 –15.8%), 18.5% (95% CI 16.6–20.7%) and 25.4% (95% CI 23.0–28.1%) at 1, 6, 12 and 24 months, respectively. Rates decreased from 98.4/100 person-years at 1 month, to 18.7/100 person-years for the 1–6 month period, 11.0/100 person-years for the 6–12 month and 9/100 person-years for the 12–24 month. They were higher in patients eligible for ART at programme entry than in those not eligible (Figure 2B).

In multivariate analyses, being LFU was associated with initial severe clinical stage (aHR=1.50, 95%CI 1.11-2.03 and 1.86, 95%CI 1.26-2.75, for clinical stage 3 or 4 compared to stage 1 or 2, for the periods 0-6 and 6-60 months respectively; Table 3). Compared to patients not eligible for ART, eligible patients had increased risk of being LFU (aHR of 1.92, 95%CI 1.30-2.82 and 2.31, 95%CI 1.49-3.56, respectively for the two periods).

Sensitivity analysis excluding patients with missing data showed similar results both for risk factors of pre-ART mortality and LFU.

Discussion

This multicentric study conducted among 2,244 children who received HIV care in four large HIV programmes in sub-Saharan Africa showed high pre-ART mortality and LFU rates among patients eligible and non-eligible for ART, especially during the early months after programme entry. During the first 6 months of pre-ART care children initially eligible for ART were 14 times more likely to die and 2 times more likely to be LFU than those ineligible.

The observed delay in ART initiation among eligible children was approximately two months. This is similar to delays reported in rural Zambia [5], but twice as long as estimates from urban programmes in Abidjan [8] and Lusaka [19] . Twenty-five percent of initially eligible patients started therapy more than five months post-enrolment and a high number of deaths and dropouts occurred in the same timeframe among children not yet initiated on ART. Various barriers to care contribute to delay ART initiation [29] and their relative importance is context dependent. First, the complexity of patient management is greater for children than for adults. Continuity and adequate paediatric HIV care are closely dependent on caregivers who might change over time. Many children may be single- or double-parent orphan [30, 31] or caregivers be also affected by HIV-related illness. Identification of reliable caregivers is therefore frequently challenging and will strongly influence delays in therapy start and compliance with treatment. Second, greater challenges are generally faced by programmes located in rural settings, including limited laboratory capacity to perform CD4 count testing, less experienced and trained health workers, or longer traveling distances to health facilities [29].

In our study, over time, a greater proportion of patients had known ART eligibility status at programme entry and among these the proportion of patients initially ART eligible decreased. Patients referred by in/out patient departments were less likely to die than those

referred by the PMTCT/VCT departments. Possible reasons might be a wider availability of CD4 testing at programme entry and increased number of experienced and trained staff. However direct (e.g. transportation cost) and indirect costs (e.g. time off work and home), the need to synchronize follow-up with other infected family members, or fear of stigma associated with HIV status disclosure may also affect paediatric diagnosis and care continuation. Finally, interviews conducted with LFU patients in Chiradzulu illustrated how a negative staff attitude could lead to care discontinuation [26]. Efforts to reduce workload, including decentralization of HIV care and VCT, task shifting to lower trained cadres and increased CD4 testing availability could contribute to improve staff work conditions and patient care in areas of high HIV prevalence.

In our evaluation, initial ART eligibility accounted for 62% of deaths and 44% of LFU, and 39.7% of deaths occurred within one month of inclusion. In two programmes in Cambodia [4], 79% of deaths occurred among eligible children not yet started on ART, and 25% of these within one month after eligibility determination. In rural Zambia, 77.8% of pre-ART deaths were reported amongst eligible children [5] and the three-month mortality rate post-enrolment was 4.5/100 person-years, which is half the rate found in eligible children in our study. Analysis of a small cohort of eligible children in Gambia showed high pre-ART mortality and attrition rates (25.7/100 and 115.7/100 person-years, respectively) [6]. No risk factors for death were identified, but young age (less than 2 years) and advance clinical stage were independently associated with increased programme attrition. Our findings also identified advanced HIV disease as predictor of both early and late deaths, factor associated with increased mortality during the early months of ART use [8, 15-19].

In the absence of ART it is estimated that 62%-89% of infected children would have died by the age of 2 years [20-22]. Children diagnosed and treated at older ages are likely to largely represent “long survivors” or “slow progressors” who did not benefit from PMTCT interventions. Today’s primary challenges are to offer integrated PMTCT in antenatal care services to avoid paediatric infections, and to ensure early infant diagnosis for infected children [23]. Services adapted to the local context [24], reinforcement of family counselling, better linkage between PMTCT and paediatric treatment programmes, wider availability of rapid diagnostic testing for HIV infection, and , availability of point-of-care CD4 count testing tools for early determination of ART eligibility, are also necessary. Meanwhile, strategies should be adopted to improve detection of HIV infection outside PMTCT programs (e.g. malnutrition and immunisation programmes), and survival among late presenters through earlier and simplified access to ART (e.g. ART start for all children younger than 5-10 years regardless of CD4 counts), concurrent management of malnutrition [23] and tuberculosis, prevention and treatment of opportunistic infections through wide administration of cotrimoxazole, and immunization. Implementation of such recommendations may improve pre-ART retention [25].

Poor initial screening, impossibility for too sick patients to return for further investigation or patients/caregivers receiving inadequate information about their condition might explain the high rates of LFU observed in our study. It is likely that many of them died before treatment could be initiated [26, 27], leading to under-estimation of mortality and overestimation of LFU rates. The high LFU rate also reflects the difficulties encountered by caregivers often also infected to attend HIV clinics [26, 28, 29]. In healthier patients, counselling sessions must emphasise the importance of regular patient monitoring of ART

eligibility status and early start of therapy. The availability of child friendly clinics where children can obtain and actively provide peer-support might also increase retention in HIV care. Further studies on barriers to care and reasons for care interruption, and implementation and evaluation of care strategies such as one-stop care services for all the members of a family could help to improve programme retention. In addition, we observed an important proportion of children with unknown eligibility status who were lost to follow-up immediately after their first visit. By not returning to care, patients might have missed opportunities for further investigations (e.g. when point-of-care CD4 count testing was not available), and so their eligibility could not be determined. Children with apparent good health (stage 1/2) and without prescribed treatment might also not return to care after the first visit. Availability of point-of-care CD4 count testing and provision of adequate counselling to guardians and children on HIV and the need for regular medical monitoring are important to reduce high rates of early follow-up.

Strengths of this analysis include its multicentric nature, a good electronic medical system covering pre-ART care and its sample size. Several limitations are to be considered when examining our findings. First, the reported median time between HIV testing and programme enrolment might be biased since it is calculated within the group of patients who enrolled in HIV care. However, we would expect this bias to be small given that counsellors referred patients for programme enrollment just after disclosing their HIV status. Second, CD4 cell count and clinical stage data were missing for some patients. Nevertheless, the results of the complete case analysis showed consistent results. Third, information related to some potential confounding factors (e.g. home distance to health facilities, parental vital status, or patient haemoglobin) was not available for analysis. Furthermore,

death was incompletely ascertained and a non-negligible proportion of patients LFU may have died [32], leading to an underestimation of mortality and overestimation of LFU. However, competing risk analyses showed concordant results.

In conclusion, our findings highlight the challenges and unmet needs related to the provision of paediatric care faced by HIV programmes in many rural areas of sub-Saharan Africa with high HIV prevalence. Strategies to minimize missed opportunities for HIV testing and to increase access to early diagnosis and treatment are necessary.

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405 **Table 1. Patient characteristics at enrolment in the HIV programmes, 2004-2010 (N=2244)**

Characteristics	N
Country, *n(%)*	
Malawi	1183 (52.7)
Uganda	475 (21.2)
Kenya	586 (26.1)
Year of inclusion	
2004-2006	1014 (45.2)
2007-2010	1230 (54.8)
Mode of entry, *n(%)*	
VCT/PMTCT	1079 (56.5)
In/Out patient	458 (24.0)
Medical referral	286 (15.0)
Other	85 (4.5)
Missing	336
Sex, *n(%)*	
Female	1184 (52.8)
Age (years)	
Median [IQR]	8 [6 – 11]
Body mass index (kg/m²)	
< 18.5	1001 (46.8)
≥ 18.5	1136 (53.2)
Missing	107
Clinical stage, *n(%)*	
1/2	1051 (56.9)
3/4	795 (43.1)
Missing	398
Diagnosis of tuberculosis, *n(%)*	223 (9.9)
CD4 cell count (cells/µL)	
Median [IQR]	409 [203 – 478]
< 50	151 (9.1)
50 – 199	258 (15.6)
200 – 349	315 (19.1)
350 – 499	258 (15.6)
≥ 500	672 (40.6)
Missing	590
Eligibility	
No	503 (29.0)
Yes	1233 (71.0)
Unknown	508

406 Note: IQR, interquartile range; PMTCT, prevention of mother to child transmission of HIV infection; VCT, voluntary counselling
407 and testing.

Table 2. Associations between individual-level factors and mortality during the 0-6 and 6-60 month pre-ART follow-up periods, 2004-2010.

Patient characteristics	0 to 6 months			6 to 60 months		
	Crude HR (95% CI)	Adjusted HR* (95% CI)	Adjusted SHR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Adjusted SHR* (95% CI)
Year of inclusion						
2004-2006	1	1		1	1	
2007-2010	0.65 (0.35 – 1.18)	2.57 (1.30-5.06)		2.47 (0.90 – 6.75)	2.17 (0.68 – 6.94)	
Mode of entry						
VCT/PMTCT	1			1	1	1
In/Out patient	0.68 (0.34 – 1.36)	-		0.51 (0.19 – 1.37)	0.12 (0.03 – 0.42)	0.13 (0.36 – 0.44)
Other	0.50 (0.18 – 1.40)			0.73 (0.20 – 2.59)	0.16 (0.03 – 0.70)	0.22 (0.54 – 0.88)
Missing	0.29 (0.83 – 1.03)			0.38 (0.07 – 1.95)	0.06 (0.01 – 0.36)	0.62 (0.10 – 0.36)
Sex						
Male	1	-		1	-	-
Female	0.78 (0.43 – 1.43)			1.21 (0.53 – 2.76)		
Age in years (per 10 unit increase)	0.96 (0.85 – 1.07)			0.95 (0.80 – 1.12)		
Body mass index (kg/m²)						
< 18.5	1	1	1	1	1	1
≥ 18.5	0.37 (0.19 – 0.71)	0.44 (0.22 – 0.87)	0.49 (0.24 – 0.99)	0.57 (0.25 – 1.28)	0.39 (0.17 – 0.90)	0.48 (0.20 – 1.17)
Missing	1.48 (0.45 – 4.88)	0.60 (0.17 – 2.17)	0.51 (0.12 – 2.06)	-	-	-
Clinical stage						
1/2	1	1	1	1		
3/4	6.90 (3.02 – 15.78)	3.75 (1.49 – 9.48)	3.60 (1.41 – 9.20)	1.67 (0.59 – 4.71)	-	-
Missing	2.61 (0.92 – 7.47)	2.29 (0.77 – 6.84)	2.45 (0.90 – 6.67)	2.31 (0.91 – 5.83)		
Diagnosis of tuberculosis						
No	1	1	1	1	1	1
Yes	3.73 (1.88 – 7.41)	1.98 (0.92 – 4.29)	2.09 (0.94 – 4.68)	4.37 (1.30 – 14.68)	6.40 (1.78 – 22.96)	6.01 (1.65 – 21.94)
CD4 cell count (cells/μL)						
< 200	1	1	1	1	1	1
≥ 200	0.45 (0.14 – 1.45)	0.63 (0.19 – 2.07)	0.77 (0.22 – 2.72)	0.45 (0.19 – 1.06)	0.05 (0.01 – 0.41)	0.05 (0.01 – 0.48)
Missing	4.07 (1.43 – 11.68)	7.07 (2.39 – 20.90)	6.36 (2.15 – 18.77)	0.10 (0.05 – 0.20)	0.06 (0.01 – 0.80)	0.05 (0.01 – 1.25)

*Models were adjusted for programme site

Note: CI, confidence interval; HR: Hazard ratio; SHR: Sub Hazard ratio; PMTCT, prevention of mother to child transmission of HIV infection; VCT, voluntary counselling and testing.

Table 3. Associations between individual-level factors and lost to follow-up during the 0-6 and 6-60 month pre-ART follow-up periods, 2004-2010.

Patient characteristics	0 to 6 months		6 to 60 months	
	Crude HR* (95% CI)	Adjusted HR* (95% CI)	Crude HR* (95% CI)	Adjusted HR* (95% CI)
Year of inclusion				
2004-2006	1	1	1	1
2007-2010	0.86 (0.67 – 1.11)	2.54 (1.86-3.47)	0.60 (0.43 – 0.83)	0.81 (0.55 – 1.19)
Mode of entry				
VCT/PMTCT	1		1	
In/Out patient	0.69 (0.50 – 0.94)	-	0.52 (0.35 – 0.79)	-
Other	0.82 (0.55 – 1.22)		0.65 (0.38 – 1.13)	
Missing	0.77 (0.51 – 1.16)		0.70 (0.40 – 1.23)	
Sex				
Male	1		1	
Female	0.81 (0.63 – 1.05)	-	0.93 (0.67 – 1.29)	-
Age in years (per 10 unit increase)	1.01 (0.97 – 1.06)		1.03 (0.97 – 1.10)	
Body mass index (kg/m²)				
< 18.5	1	1	1	
≥ 18.5	0.76 (0.59 – 0.99)	0.79 (0.60 – 1.03)	0.91 (0.65 – 1.28)	-
Missing	2.71 (1.71 – 4.29)	1.95 (1.18 – 3.23)	1.87 (0.74 – 4.68)	
Clinical stage				
1/2	1	1	1	1
3/4	1.52 (1.16 – 2.00)	1.50 (1.11 – 2.03)	1.91 (1.31 – 2.76)	1.86 (1.26 – 2.75)
Missing	0.83 (0.57 – 1.22)	0.88 (0.59 – 1.33)	1.25 (0.82 – 1.88)	1.34 (0.86 – 2.07)
Diagnosis of tuberculosis				
No	1		1	
Yes	1.25 (0.82 – 1.89)	-	1.33 (0.58 – 3.01)	-
CD4 cell count (cells/μL)				
< 200	1	1		
≥ 200	1.38 (0.75 – 2.53)	1.43 (0.77 – 2.65)	-	-
Missing	6.57 (3.63 – 11.86)	9.03 (4.93 – 16.56)		

*Models were adjusted for programme site

Note: CI, confidence interval; HR: Hazard rate ratio; PMTCT, prevention of mother to child transmission of HIV infection; VCT, voluntary counselling and testing.

Figures

Figure 1. Flow chart of 5-14 years old patients included in the analysis, Malawi, Kenya and Uganda, 2004-2010.

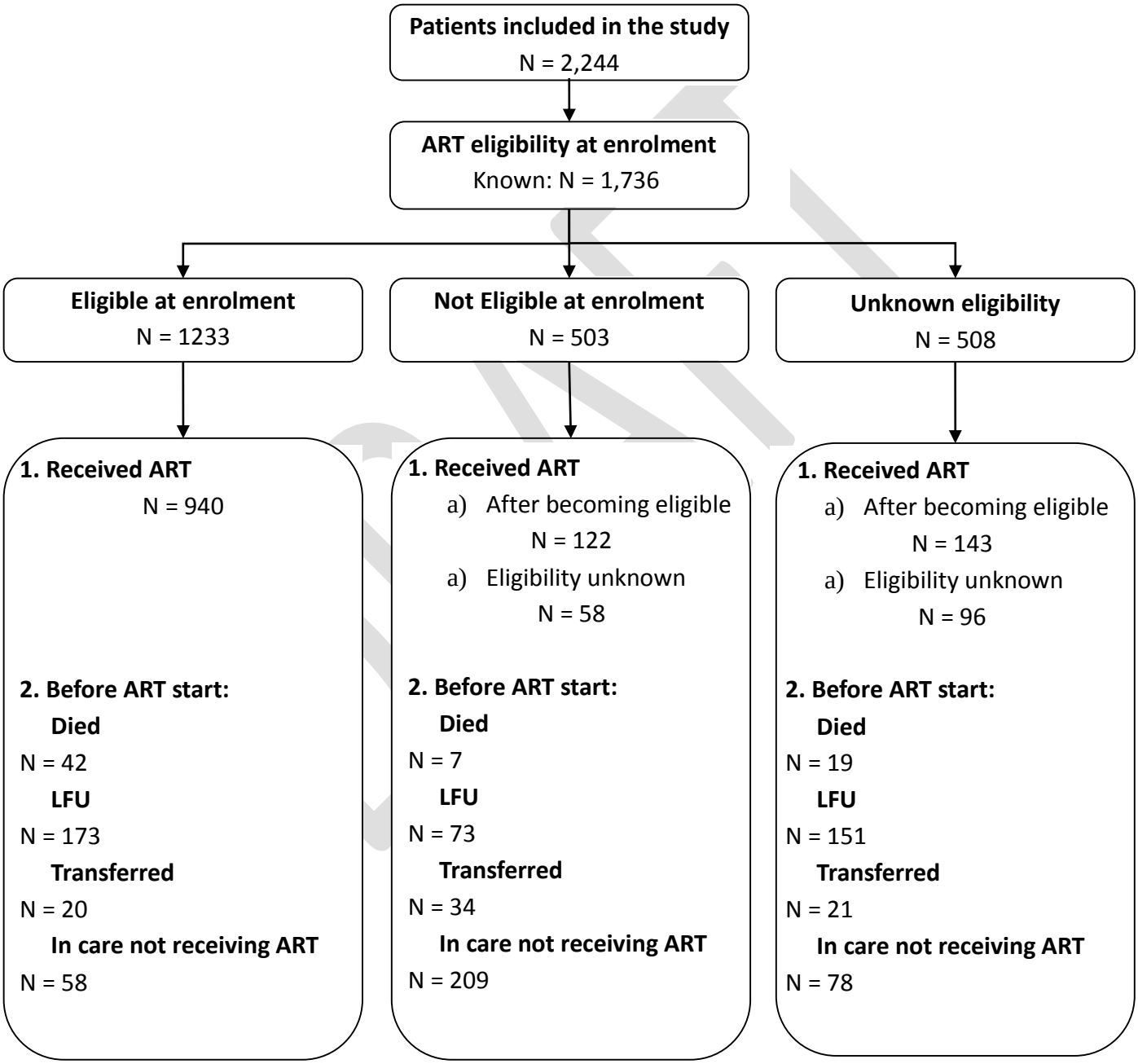

Figure 2. Kaplan-Meier estimates of (a) mortality and (b) lost to follow-up, stratified by eligibility status at enrolment, Malawi, Uganda, Kenya, 2004-2010.