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Earlier antiretroviral therapy initiation and decreasing mortality among HIV-infected infants initiating antiretroviral therapy within 3 months of age in South Africa, 2006-2017

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Abstract

Introduction: Early infant diagnosis of HIV and antiretroviral therapy (ART) have been rapidly scaled-up. We investigated the effect of expanded access to early ART on the characteristics and outcomes of infants initiating ART.

Methods: From nine cohorts within the International epidemiologic Databases to Evaluate AIDS - Southern Africa collaboration, we included infants with HIV initiating ART ≤3 months of age between 2006-2017. We report ART initiation characteristics and the probability of mortality, loss to follow-up (LTFU) and transfer out (TFO) after 6 months on ART, and assessed factors associated with mortality and LTFU.

Results: A total of 1847 infants started ART at a median age of 60 days (interquartile range (IQR) 29-77) and CD4 percentage (%) of 27% (IQR 18%-38%). Across ART initiation periods 2006-2009 to 2013-2017, ART initiation age decreased from 68 (IQR 53-81) to 45 days (IQR 7-71) ($p<0.001$), median CD4% improved from 22% (IQR 15%-34%) to 32% (IQR 22-43) ($p<0.001$) and the proportion with WHO disease stage 3 or 4 declined from 81.6% to 32.7% ($p<0.001$). Overall, 5.0% of infants died, 20.4% became LTFU and 8.5% were TFO six months after ART start. Mortality was 10.6% (7.8%-14.4%) in 2006-2009 and 4.6% (3.1%-6.7%) in 2013-2017 ($p<0.001$), with similar LTFU across calendar periods ($p=0.274$). Pre-treatment weight-for-age Z-score < -2 was associated with higher mortality.

Conclusions: HIV-infected infants are starting ART younger and healthier with associated declines in mortality. However, the risk of mortality remained undesirably high in recent years. Focused interventions are needed to optimize the benefits of earlier diagnosis and treatment.

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Introduction

In sub-Saharan Africa, an estimated 140,000 new HIV infections and 73,000 AIDS-related deaths occurred in 2018 among children 0-9 years of age.[1] Compared to older children, HIV-infected (HIV+) infants are prone to high early mortality and without ART, 50% will die before their second birthday.[2] Complexities related to testing, age and weight-related drug changes, rifampicin co-treatment of tuberculosis and limited drug formulations make infants a highly vulnerable population.

The World Health Organization's (WHO) guidelines for paediatric ART initiation has shifted from clinical and CD4-based criteria to immediate ART for all (Universal ART). In 2008, universal ART was recommended for all HIV+ infants <12 months of age based on findings from the landmark Children with HIV Early antiRetroviral (CHER) trial.[3, 4] In 2010, South Africa adopted universal ART for children under 2 years of age. Furthermore, guidelines for lifelong universal ART for all pregnant and breastfeeding women living with HIV (so-called "Option B+") [5] and universal testing for HIV-exposed infants at birth were implemented in 2013 and 2015, respectively.[6] Consequently, by 2017, prevention of mother-to-child transmission of HIV (PMTCT) service uptake was >95%, the national coverage of early infant diagnosis (EID) and birth HIV testing uptake were both >90%, and paediatric ART coverage was >75%.[1, 7]

With expanded ART access, the demographic and clinical characteristics of recently infected infants may differ from those infected before the introduction of Option B+ and early testing. For example, prematurity, low birth weight (LBW), immunosuppression and comorbidities may be more prevalent in those becoming HIV-infected despite widespread coverage of Option B+. Of note, infants with these "high risk" characteristics were excluded from the CHER trial therefore, the survival benefit may not be generalizable to current programmatic settings,

especially in resource-limited settings (RLS) where infants may present for treatment with advanced HIV disease.[8-10] While the outcomes of infants infected before the availability of EID and early ART have been described,[10-13] there are limited data on infants initiating early ART outside research-controlled settings, in the context of improved EID practices and widespread access to ART. Using observational data, we examined temporal trends in the characteristics and treatment outcomes of HIV+ infants.

Methods

Study setting and participants

We conducted a retrospective cohort study using data from nine IeDEA-SA cohorts in South Africa. IeDEA is a global research consortium which collects routine anonymised data on patients receiving HIV care and treatment.[14] Eight of the nine sites included are mostly in urban areas representing primary, secondary and tertiary levels, while one site represents a private health sector facility. All sites contributing data to this study have relevant institutional and ethical approval.

We included ART-naïve infants (except for exposure to PMTCT drugs), initiating ART ≤3 months of age from January 2006 (first WHO treatment guidelines for children) to November 2017. To better understand the effect of changing WHO eligibility criteria for ART initiation, and expansion of PMTCT programmes between 2006 and 2017, infants were grouped according to the calendar year of ART initiation: 2006-2009, 2010-2012 and 2013-2017 representing the implementation of WHO ART eligibility for all HIV-infected children <2 years in 2010 and Option B+ in 2013 respectively. The study entry point was defined as the earliest date of ART initiation at the IeDEA-SA clinical site. We defined ART as a combination ≥3 antiretroviral drugs from ≥2 different drug classes. The recommended first-line regimen for children <3 years

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of age prior to 2010 was stavudine, lamivudine and lopinavir/ritonavir (LPV/r). From 2010, national treatment guidelines recommended that abacavir replace stavudine in the first-line regimen. Guidelines also recommend that newborns receive zidovudine, lamivudine and nevirapine for the first month or until >3kg.

Outcomes and key variable definitions

Our primary analysis described ART initiation characteristics and outcomes of mortality, loss to follow-up (LTFU) and transfer out (TFO) to other facilities by six, compared across calendar periods. We also described weight-for-age z-score (WAZ) improvement in those retained for six months after ART initiation. Mortality included all-cause mortality as documented in the database. LTFU was defined as not having any documented clinic visit or laboratory result within a window period of 4-9 months after ART initiation, irrespective of whether the child returned to care >9 months after ART initiation. We further distinguished infants who had no visits after the date of ART initiation for up to nine months as having 'no follow up' while those with ≥1 subsequent visit within the first three months on ART but with no visit between 4-9 months after ART initiation were classified as 'LTFU but with subsequent follow up on ART'.[15] WAZ improvement by 6 months on ART was assessed using the WAZ closest to six months after ART start (window 4-9 months). Analysis of outcomes was limited to infants starting ART ≥6 months before database closure. Follow-up was right-censored at the earliest of death, last clinic visit (for patients LTFU), date of transfer outside the programme or 6 months after ART start.

WAZ was calculated using the WHO Child Growth Reference Standards.[16] We defined underweight as WAZ ≤−2 and severely underweight as WAZ ≤−3. Immunosuppression was classified using CD4% as severe (<15), moderate (15–24%), or absent (>25%).[17] When describing weight measurements and laboratory values at ART initiation, we selected the

measurement closest to ART start date within a window of -3 weeks to +1 month for WAZ and -6 months to +2 weeks after ART start for viral load, CD4 counts and percentages.

Statistical analysis

We compared ART initiation characteristics across calendar periods using the Chi-square or Fisher's exact test (in the case of sparse data) and Kruskal-Wallis test for categorical and continuous variables, respectively. We used Kaplan-Meier methods to estimate the probability of mortality, LTFU and TFO and compared survival among various categories using the Log-rank test. Due to the interdependence of mortality, LTFU and TFO, we also conducted competing risks analysis to calculate the cumulative incidence functions for these outcomes.

We used Cox regression to determine ART initiation characteristics associated with mortality and LTFU. Patient-level covariates included in the models were selected *a priori* as potential confounders based on their clinical relevance and data availability and included: age, sex, clinical stage, WAZ <-2, $\log_{10}$ viral load, CD4 percentage or immunosuppression level, WHO disease stage, PMTCT exposure, year of ART initiation (2006-2009, 2010-2012 and >2013). Adjusted Cox regression models were stratified by clinical site to account for heterogeneity.

We addressed missing baseline data for WAZ, viral load, WHO disease stage and CD4 cell counts and percentages using multiple imputation methods. The imputation model relied on the assumption of data missing at random and included all ART initiation characteristics, cohort, year of ART initiation and outcome variables. We generated 10 imputed dataset and combined estimates using Rubin Rules.[18] We performed a sensitivity analysis to assess predictors of mortality including only patients with complete case data. All statistical analyses were performed using STATA 15.0 (STATA Corporation, College Station, TX).

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Results

ART initiation characteristics

Between 2006-2017, 17,854 HIV+ children <5 years old initiated ART in the IeDEA-SA sites in South Africa (Figure 1). Among these, the proportion starting ART ≤3 months of age increased from 6.3% to 20.5% in 2006-09 and 2013-17 respectively (p<0.001).. The median age was 60 days (IQR: 29-77) and differed substantially by calendar period, ranging from 68 days in 2006-09 to 45 days in 2013-17 (p <0.001). There was a marked increase in the proportion of infants starting treatment within one month of age (vs. 7% [2006-10], 14% [2010-13] and 44% [2013-17]). The median CD4% was 27%, improving from 22% in 2006-09 to 32% in 2013-17 (p <0.001).There was a pattern towards an increase in the proportion of females and median log viral load over time. Half of all infants were classified with WHO disease stage three or four, however, this proportion decreased substantially over time (81.6% [2006-09] vs. 32.7% [2013-17]; P<0.001). (Table 1). Compared to infants starting ART in the first month of age (0-30 days), those starting between 31-60 days and 61-90 days of age were more likely to be underweight (WAZ <-2) (38.5% vs. 60.6% and 60.1%; P<0.001).

Programme outcomes over time

Among 1692 infants who started ART at least 6 months before individual cohort database closure dates, 86 (5.0%) died, 353 (20.8%) became LTFU and 144 (10.2%) were TFO. The 6-month

cumulative probabilities of mortality (95% confidence interval [CI]), LTFU and TFO were 6.4% (5.2-7.9), 21.5% (19.4-23.3) and 10.6% (9.0-12.3) respectively. Mortality probability was highest among infants initiating ART in 2006-09 (10.6% [7.8-14.3]) compared to 2013-2017 (4.6% [3.1-6.7]), Log-rank test $p<0.001$). LTFU remained similar across calendar period, ranging from 23.8% (20.2-28.0) in 2006-2009 to 21.0% (18.1-24.3) in 2013-2017 (Log-rank test $p=0.2746$). Competing risk analysis yielded similar estimates as shown in Figure 2 and Supplementary Table 1.

The median follow-up time for infants that died was 33 (21-88) days, for LTFU was 0 (0-18) days and for TFO was 45 (12-94) days. For 2006-2009 period, death occurred at a median of 27 (15-57) days versus 45 (21-85) days in the latest period. The median age at death was 94 days (IQR: 79-134), with no significant difference across ART initiation time periods ($P=0.4655$). In addition, 61.5% of infants that died initiated treatment between 61-91 days of age. Among those LTFU, 74% did not return for a clinic visit after the date of ART initiation for up to 9 months, while 26% returned for a subsequent visit after initiating ART (within 3 months on ART) and thereafter were LTFU from 3-9 months following ART initiation.

Risk factors for mortality and LTFU

Relative to ART start between 2006-2009, the unadjusted mortality hazard ratio (uHR) was lower for infants starting ART in 2010-12 (0.47 [0.27-0.79]) and 2013-17 (0.46 [0.28-0.75]) (Table 2), however this effect was attenuated after adjusting for disease severity at ART start. Compared to having WAZ >-2, infants with WAZ ≤-2 had a 1.7-fold (Adjusted hazard ratio [aHR], 1.74; 95% CI: 1.07- 2.81) increased risk of death (Table 2). We observed decreasing risk LTFU (i.e. no follow-up and LTFU but with subsequent follow-up on ART) over time. Initiating ART between 2010-2012 and after 2013 were associated with a decreased unadjusted hazard of LTFU

(aHR 0.54, 95% CI: 0.40-0.73 and aHR: 0.46, 95% CI: 0.33-0.62, respectively), compared to 2006-2009.

Infants with unknown maternal or infant PMTCT status at ART initiation had a 2.4-fold increased risk of being LTFU immediately following the date of ART initiation (no follow up) (aHR: 2.43, 95% CI: 1.32-4.59). None of the infant ART initiation characteristics included was associated with LTFU after at least one subsequent visit after ART initiation (Supplementary Table 2). Overall, similar estimates were identified when complete case analysis was conducted, except for no decrease in risk of LTFU in the most recent calendar period (Supplementary Table 3).

Weight improvement

At ART initiation, the median WAZ (IQR) at initiation was -2.4 (-3.7 to -1.1), varying significantly across calendar periods ($p<0.001$), 56% of all infants had WAZ $\leq$-2 (underweight =19.3% plus severely underweight =34.8%). Following 6 months on ART, the median WAZ was -1.19 (-2.3 to -0.3) which did not differ by calendar period of ART initiation ($p=0.949$); 30% of infants were underweight.

Discussion

In this study of infants with HIV starting ART $\leq$3 months of age, we found that an increasing proportion of infants started ART at younger ages and with less advanced HIV disease. Overall, mortality was 5.0% with marked differences between the calendar periods. Although mortality was halved from 2010 onwards, mortality remained at 4.1% after 2013. An unchanging proportion of 1 in 5 infants were LTFU after 6 months of ART, with nearly three-quarters of those having no follow-up after their ART initiation visit. Declining mortality is likely mediated

by earlier ART initiation reflecting the real-world benefit of the shift to universal ART for infants and simultaneous expansion of EID access, particularly birth testing in South Africa.

Characteristics of children starting ART improved across calendar periods. A marked increase in the proportion of infants ≤1 month of age at initiation was a major driver of decreasing age at ART start. We attribute this finding to improved EID services and the resulting high coverage of >90% in South Africa following introduction of universal birth testing in 2015. However, considering the recent context of expanded EID and treatment programmes, infants infected after 2013 still started ART relatively late at a median age of 45 days. Similar to previous findings, we found infant CD4 percentages improved over time [10, 12]

Infants acquiring HIV despite the availability of PMTCT are more likely to be those missed by PMTCT programmes, who present for testing when they become sick rather than through routine infant follow-up.[19] For example, infants initiating ART between 61-90 days old were more likely to be underweight than those initiating before 30 days old (57% vs 38%) and underweight infants were more likely to die.[10, 20] This suggests that older infants are those who missed earlier testing, or were infected during the early postpartum period and only present to care with advanced disease and hence higher risk of mortality. This partially explains the ongoing burden of advanced disease despite high birth testing coverage among those known to the PMTCT programme. The national expansion of PMTCT (>95%) was reflected in our study as the proportion of infected infants with PMTCT exposure doubled in the latest cohort. Compared to the era of limited access to PMTCT, recent peri-and post-natal transmissions may be occurring among an emerging vulnerable population of mothers. These women may have either not engaged with the health system or were not virally suppressed despite accessing care due to complex social and medical challenges that influence health-seeking behaviour and ART adherence.

Previous ART implementation studies in infants before expansion of early diagnosis and ART for prevention and treatment suggests a trend towards decreasing long-term mortality over time. Our findings extends existing evidence to include trends in short-term mortality in infected early-treated infants.[10, 21, 22] The effect of lower mortality over time was not retained after adjusting for disease severity, suggesting that lower mortality was mediated by earlier ART initiation and improved infant characteristics. The probability of survival for period 2013-2017 was 93%, lower than the estimated 6-month survival probability of 97% for all South African infants.[23] The true mortality difference between children with and without HIV is likely even greater due to the inherent survival bias in our cohort and our follow-up starting at ART initiation rather than birth. An estimated 12-months mortality of 14%has been reported in a cohort of birth-identified HIV-infected infants, suggesting significant mortality despite ART in this cohort.[24]

The CHER trial enrolled infants starting ART <12 weeks of age (excluding infants with a birth weight below 2kg, advanced HIV and CD4 depletion) and followed up for a median of 40 weeks comparing early and deferred ART.[4] Mortality in our population during the 2013-17 period was 4.6%, compared to 4.0% reported in the CHER trial arm for immediate ART. Although higher mortality rates would be expected in our population, a shorter follow-up period and high LTFU may have masked true mortality. While it is concerning that mortality did not decline further during the latest period (compared to 2010-12) when both Option B+ and birth EID were implemented, characteristics such as prematurity and associated complications, and infectious comorbidities may have contributed to poorer outcomes. Furthermore, since we only measured mortality after ART start, it is possible that infants who previously would have died before being diagnosed and/or starting ART are now initiating ART earlier, and that pre-ART mortality has shifted to mortality after early ART initiation. These explanations are supported by another study which reported that 15% more HIV+ infants were lost from the ART programme by one year among those who started after 2012 relative to those starting before 2010.[25]

More than half of deaths occurred in the first three months of ART initiation and this pattern was most pronounced in the 2006-2009 cohort, similar to earlier studies.[26] While high rates of bacteraemia and IRIS have been associated with high early mortality, earlier ART start with higher CD4 percentages has likely resulted in IRIS becoming less common.[27]

The high proportion of infants with no follow up is particularly concerning. Increased mobility and poor HIV service retention soon after delivery among women living with HIV are well-documented and contribute to low retention of infants soon after initiating treatment.[28] While poor documentation of transfer between health care facilities may underestimate retention, high early LTFU may contribute to mortality under-ascertainment. In this respect, although overall LTFU didn't decrease over time, the risk of LTFU after adjustment for disease severity reduced in recent years suggesting that true LTFU may be reduced. Improved focus on retention and shift towards individualised care may be more feasible in the context of a decreased overall burden of paediatric HIV. As with mortality, it is possible that that pre-ART LTFU has been shifted to LTFU on ART following the implementation of birth diagnosis and universal ART.

To our knowledge, this is the largest study of early infant ART outcomes in sub-Saharan Africa. This study includes data from several routine care cohorts representing different levels of health care in South Africa. Additionally, the study period covers several guideline periods, allowing assessment of the influence of guideline changes while reflecting the realities of routine resource-limited settings. The routine nature of the settings from which data was collected is evident from the amount of missing data and lack of data on PMTCT, maternal socioeconomic factors and comorbidities such as tuberculosis may have led to residual confounding. We found an increased risk of death among underweight infants but could not assess the extent to which prematurity and low birthweight are responsible for low WAZ due to limited data on gestational age at birth. There is a chance of survival bias in our selected cohort which may have led to an under-estimation of mortality.

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Conclusions

There have been improvements in infant ART initiation characteristics with related decrease in mortality over time. However, early death and LTFU remains unacceptably high. Considering the risk of mortality did not decrease further after 2010, there is a need to better understand the specific health-care needs of this population of infants who continue to acquire HIV despite widespread PMTCT and ART access and uptake.

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Contributors

VI and MD developed and wrote the analysis concept and plan. VI conducted the analyses and interpreted the results with critical input from, KT, BE, HR, AB, GF, ME, FT, RW, LF, MC and MD. VI wrote the first draft of the manuscript; all authors contributed to manuscript writing and review.

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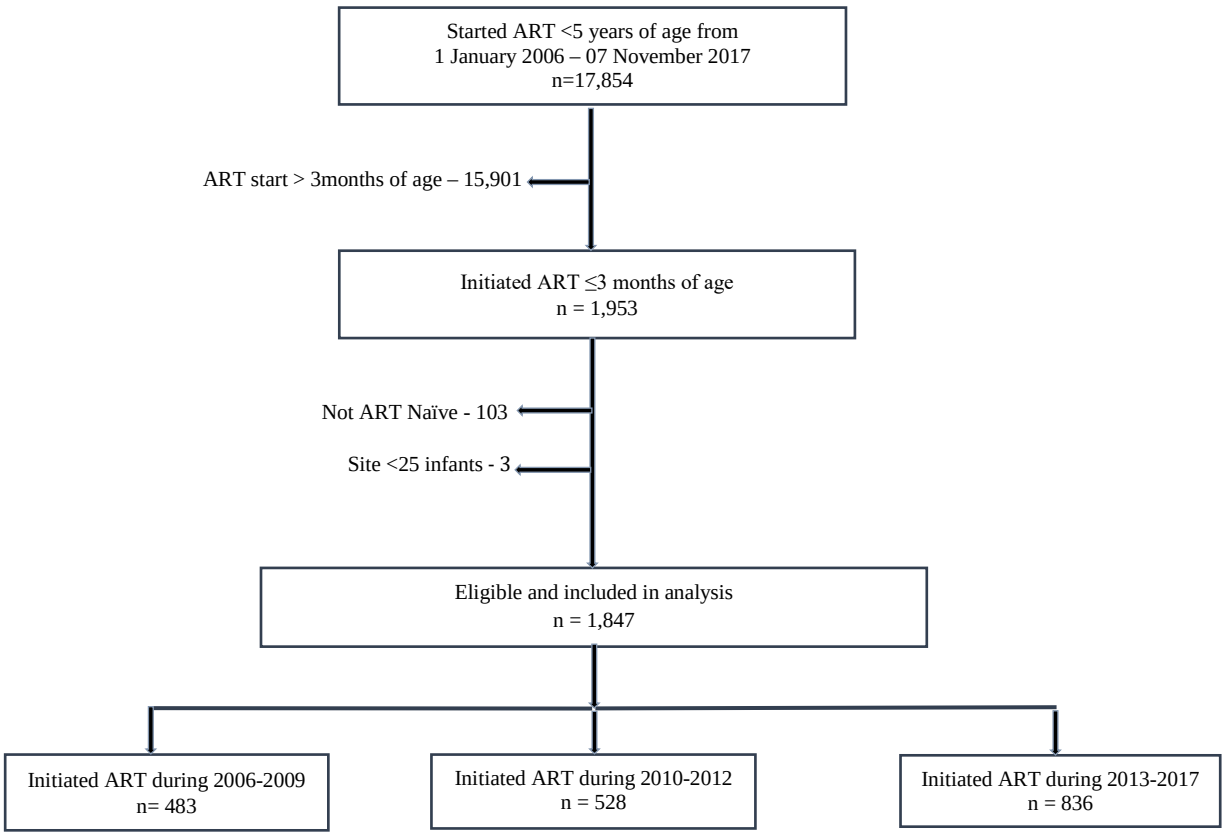

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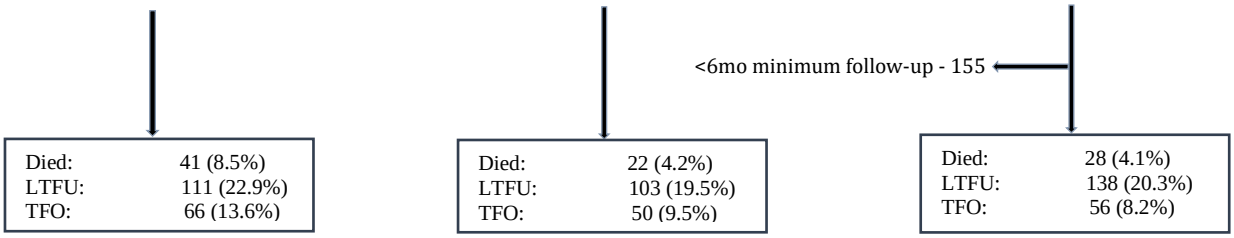

Figure 1: Flow chart describing participant selection and outcomes of infants with HIV initiating ART ≤3 months of age from 2006-2017

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Table 1. Characteristics of infants who initiated antiretroviral therapy ≤3 months of age across South Africa

Characteristics	Overall N= 1847	2006-2009 N=483	2010-2012 N=528	2013-2017 N= 836	*p*
Age at ART start (days)	60 (29-77)	68 (53-81)	67 (46-80)	45 (7-71)	<0.001
Age category					
0-30 days	479 (25.9)	34 (7.0)	77 (14.5)	368 (44.0)	<0.001
31-60 days	464 (25.1)	155 (32.1)	141 (26.7)	168 (20.1)	
60-90 days	905 (48.9)	294 (60.8)	310 (58.7)	300 (35.8)	
Female	1028 (55.6)	250 (51.8)	317 (60.0)	461 (55.1)	<0.031
CD4 count (cells/μL)	1073 (407-1955)	899 (396-1718)	1274 (487-2028)	1149 (350-2070)	<0.035
CD4 percentage	27 (18-38)	22 (15-33)	26.2 (18-36)	32 (22-43)	<0.001
CD4% for age <30 days	42 (27-51)	21 (16-28)	38.6 (24-51)	44.3 (31-52)	0.005
CD4% for 31-60 days	27 (19-39)	26 (18-38)	26 (16-40)	32 (23-40)	0.053
CD4% for 61-90 days	24 (16-33)	21 (14-31)	24 (18.-33)	26 (16-33)	<0.001
Missing, N (%)	817 (44)	156 (32)	188 (35)	473 (56)	
Immunosuppression					
> 25% (none)	556 (54)	143 (43)	177 (51.9)	246 (67.6)	<0.001
> 15 - ≤ 25% (moderate)	284 (27)	104 (31)	110 (32.3)	70 (19.2)	
≤ 15% (severe)	182 (17)	80 (24)	54 (15.8)	48 (13.2)	
Missing, N (%)	817 (44)	156 (32)	188 (35.6)	473 (56.5)	
Log_{10} viral load	5.8 (4-6)	5.0 (5-6)	6.0 (5.0-6.6)	5.3 (3.8-6.3)	<0.001
Viral load (copies/ml)					
<100,000	253 (27.4)	47 (15.4)	63 (22.8)	143 (41.7)	<0.001
>100,000- 1 Million	282 (30.5)	125 (40.9)	72 (26.1)	85 (24.7)	
>1 Million	389 (42.1)	133 (43.6)	141 (51.1)	115 (33.5)	
Missing, N (%)	923 (44.9)	178 (36.8)	252 (47.7)	493 (58.9)	
WHO clinical stage					
I/II	592 (47.6)	65 (18.4)	152 (45.7)	375 (67.3)	<0.001
III/IV	652 (52.5)	289 (81.6)	181 (54.6)	182 (32.7)	
Missing, N (%)	604 (32.7)	129 (26.7)	196 (37.1)	279 (33.3)	
WAZ	-2.4 (-3.7 - -1.1)	-2.9 (-4.2 - -1.7)	-2.3 (-3.6 - -1.0)	-1.7 (-3.2 - -0.5)	<0.001
WAZ category					
<-3	316 (34.8)	146 (43.7)	94 (32.6)	76 (26.6)	<0.001
- 3 to -2	175 (19.3)	70 (21.1)	62 (21.5)	43 (15.0)	
>-2	418 (45.9)	118 (35.3)	132 (45.8)	167 (58.3)	
Missing, N (%)	940 (50.9)	149 (30.8)	241 (45.6)	550 (65.7)	
PMTCT exposure[#]					
No	952(51.5)	197 (40.8)	250 (47.3)	505 (60.4)	<0.001
Yes	233 (12.6)	43 (8.9)	38 (7.2)	152 (18.2)	
Unknown	662 (35.8)	243 (50.3)	240 (45.5)	179 (21.4)	

PMTCT, Prevention of mother-to-child transmission of HIV; ART, Antiretroviral therapy; WAZ, Weight-for-age Z-score; WHO, World Health Organization

*P-values were derived from Chi-square and Kruskal-Wallis tests, where appropriate. Values are given as number (percentage) or median (interquartile range). [#]Maternal or infant PMTCT exposure

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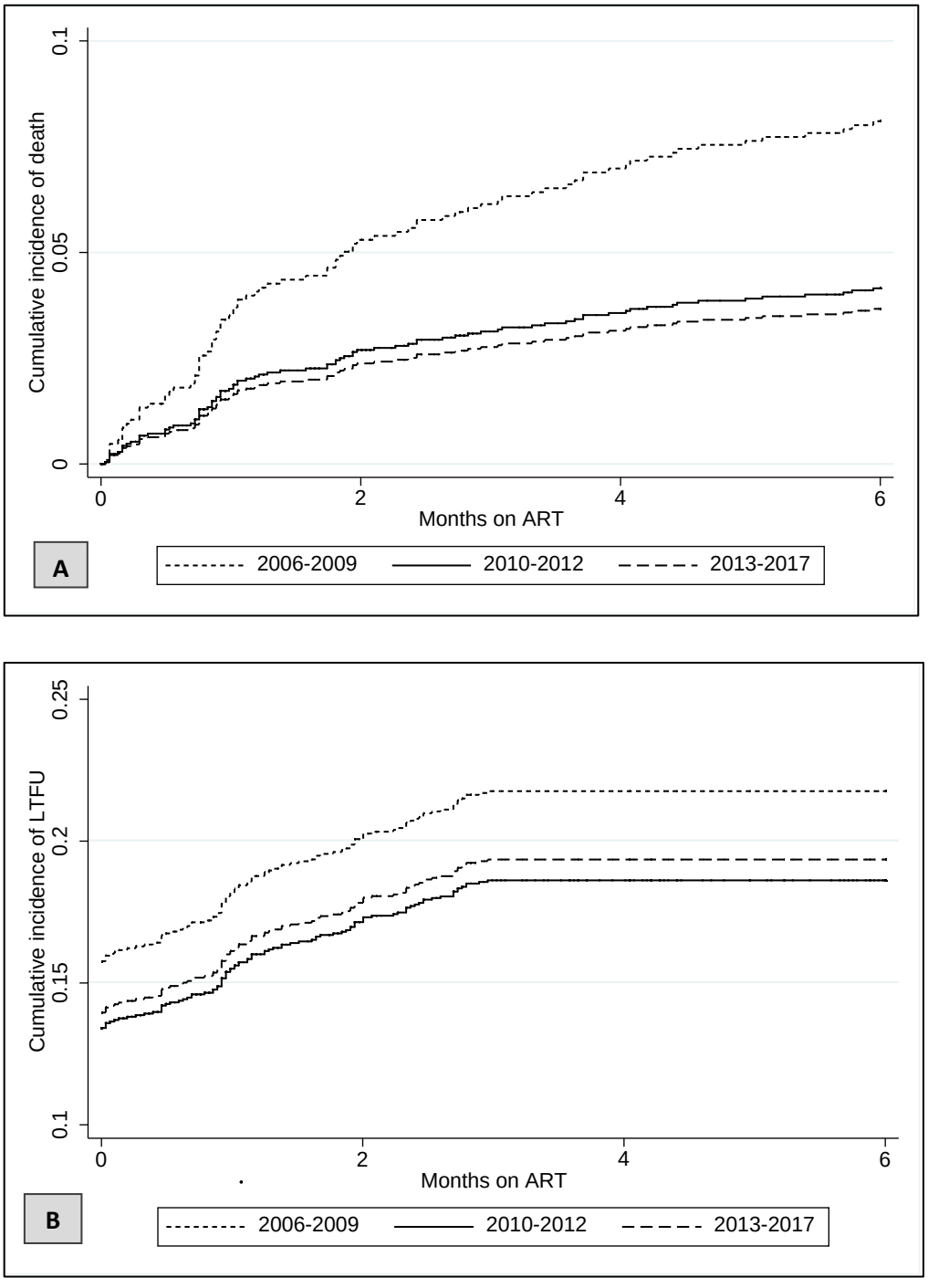

Figure 2. Cumulative incidence functions stratified by calendar period of ART initiation for:

(A) Mortality accounting for LTFU and TFO as competing events **(B)** LTFU accounting for

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death and TFO as competing events. Plot shows time to LTFU defined as no visit from 4-9 months on treatment. ART, Antiretroviral therapypy; LTFU, Loss to follow-up

Table 2. Cox proportional hazards model of imputed dataset stratified by cohort: Infant characteristics associated with mortality and loss to follow-up within the first 6 months on ART (n=1692)

	Mortality		Loss to follow-up	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Age in weeks	1.47 (0.89-2.45)	0.95 (0.53-1.71)	0.93 (0.74-1.17)	0.89 (0.68-1.15)
Female	0.68 (0.44-1.02)	0.70 (0.46-1.07)	0.89 (0.72-1.09)	0.88 (0.71-1.09)
ART initiation year				
2006-2009	Ref		Ref	
2010-2012	0.47 (0.27-0.79)	0.76 (0.42-1.36)	0.77 (0.59-1.01)	0.54 (0.40-0.73)
2013-2017	0.46 (0.28-0.75)	0.98 (0.54-1.75)	0.80 (0.62-1.03)	0.46 (0.33-0.62)
WHO disease stage				
I/II	Ref		Ref	
III/IV	1.85 (1.14-2.99)	1.08 (0.61-1.91)	0.87 (0.65-1.14)	0.91 (0.65-1.28)
CD4 percentage	0.98 (0.96-0.99)	0.98 (0.96-1.00)	0.99 (0.98-1.00)	1.00 (0.99-1.01)
WAZ				
>-2	Ref		Ref	
≤-2	2.43 (1.53-3.84)	1.74 (1.07-2.81)	0.93 (0.70-1.23)	0.95 (0.71-1.26)
Log viral load	1.38 (1.07-1.58)	1.14 (0.89-1.46)	0.97 (0.88-1.08)	1.02 (0.92-1.13)
PMTCT exposure				
No	Ref		Ref	
Yes	1.17 (0.74-1.85)	0.87 (0.50-1.49)	0.59 (0.46-0.77)	1.05 (0.61-1.69)
Unknown	1.10 (0.62-1.97)	1.20 (0.50-2.86)	0.83 (0.62-1.11)	1.08 (0.65-1.78)

CI, confidence interval; HR, hazard ratio; WAZ, weight-for-age z-score; WHO
*Status of infant exposure to maternal or infant PMTCT

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