Effect of antiretroviral therapy care interruptions on mortality in children living with HIV: cohort study from Southern Africa

Running head: ART interruptions in HIV infected children

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Abstract

Objective: To evaluate the characteristics and outcomes of HIV-infected children that have care interruptions, during which the child's health status and use of medication is unknown.

Design: We included data on children initiating ART between 2004 and 2016 at <16 years old at 16 International Epidemiologic Databases to Evaluate AIDS Southern Africa cohorts. Children were classified as loss to follow up (LTFU) if they had not attended clinic for >180 days. Children had a care interruption if they were classified as LTFU, and subsequently returned to care. Children who died within 180 days of ART start were excluded.

Methods: The main outcome was all cause mortality. Two exposed groups were considered: those with a first care interruption within the first six months on ART, and those with a first care interruption after six months on ART. Adjusted hazard ratios were determined using a Cox regression model.

Results: Among 53,674 children included, 23,437 (44%) had a care interruption, of which 10,629 (20%) had a first care interruption within six months on ART and 12,808 (24%) had a first care interruption after six months on ART. Increased mortality was associated with a care interruption within six months on ART (adjusted hazard ratio (AHR) = 1.52, 95% CI 1.12-2.04) but not with a care interruption after six months on ART (AHR = 1.05, 95% CI 0.77-1.44).

Conclusions: The findings suggest that strengthening retention of children in care in the early period after ART initiation is critical to improving paediatric ART outcomes.

Keywords: Loss-to-follow up, Care Interruption, HIV, Children, antiretroviral therapy, ART

Introduction

In 2018, 1.7 million children (<15 years) globally [1] were estimated to be living with HIV. Access to paediatric antiretroviral therapy (ART) has dramatically improved, and 54% of children had access to ART in 2018 [2]. Nevertheless, approximately 100,000 children died of AIDS in 2018 [1]. This is at least partly due to loss-to-follow-up (LTFU) which is estimated to be high among children initiating ART in Southern Africa, ranging from 9% (estimate from 2000-2009 [3]) to 25% (estimate from 2004-2015 [4]), with the potential for drug resistance, opportunistic infections and viral failure.

Owing to challenges in tracing those LTFU, the true status of patients LTFU is unknown – some may be misclassified as LTFU owing to incorrect recording of visits, whilst others have died, silently transferred, or interrupted care (either short-term with later return to care or sustained loss of contact in a patient who remains alive but out of care) [5]. In the latter two situations, while the child is 'lost' they can be considered to be experiencing a care interruption. During this period, they may have completely interrupted treatment or may continue taking the existing treatment until medication is no longer available, or share medication with another person in the household [6]. These children are likely at increased risk for poor outcomes, given that stopping ART – even for a short period - is associated with a significant decrease in CD4% or CD4 count [7-10], and an increase in HIV-1 RNA [8]. Patients who become LTFU are also more likely to develop drug resistance compared to those that remain in care, reducing the number of effective treatment options [11]. Even if the patient continues to take medication, the lack of routine clinical and laboratory monitoring prevents the clinical care provider from identifying treatment failure, prevention and treatment of AIDS-related illnesses, and prevention of progression to AIDS [12]. Patients with care interruptions may therefore be at increased risk of death either while out of care or after returning to care.

There are few known studies assessing the long-term HIV outcomes of children that have had a care interruption. Ardura-Garcia et al., traced children on ART who were classified as LTFU and found children with ART gaps had an increased risk of stopping ART at study end, compared to those traced and found to be alive on ART. They did not estimate the association with mortality owing to the small number of children that died [6]. Ndiaye et al. found that adults returning to care after being LTFU were five times more likely to die than patients who attended clinic regularly [13]. In contrast, Ahonkhai et al. found that the majority of adults with care interruptions had a suppressed viral load and increased CD4 count when returning to care, potentially indicating they had continued taking ART during the interruption [14]. However, studies in adults cannot be generalised to children, given the different reasons for a care interruption, and the more rapid disease progression in young children in the absence of treatment [15, 16]. We examined the characteristics and outcomes of children that have had a care interruption in a large Southern African cohort, and assessed the association between a care interruption and mortality. We hypothesised that a care interruption is associated with increased mortality after returning to care.

Methods

Setting and design

We used cohort data collected prospectively as part of the International Epidemiologic Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration, comprising cohorts in Lesotho, Malawi, Mozambique, South Africa, Zambia, and Zimbabwe [17, 18]. Routine data containing information on clinic visit date, status of child (alive/ dead/ transferred out), and other variables is collected prospectively at each site at ART initiation, and every follow-up visit, using standard definitions. De-identified data is transferred to data centres at the Universities of Bern, Switzerland and Cape Town, South Africa, where it is merged [17]. Supplementary Table 1, http://links.lww.com/QAD/C456 summarises details of the 16 cohorts included across 126 individual health facilities.

Exposure and Outcome

The primary outcome was all-cause mortality, determined based on clinic data. There was no standardised programme of routine active tracing of patients at sites, nor linkage to vital registration systems. Children were classified as LTFU if they had not attended the clinic for >180 days. We considered children to have a "care interruption" if they were classified as LTFU (i.e. out of care > 180 days), and then later returned to care (Figure 1a). We used 180 days as clinic visits may be up to six months apart in some sites, and 180 days has been recommended for correctly classifying patients as LTFU [19, 20]. Children are presumed to be in care until a "theoretical next visit date", defined as 180 days since the last clinic visit.

We split children with a care interruption into two categories based on the timing of only the first interruption: those with their last clinic visit within the first six months on ART, and those with their last clinic visit after more than six months on ART. The rationale for this split was that children lost after more than six months on ART are more likely to be virally suppressed at the time of loss (and therefore have different characteristics to those lost within 6 months on ART), and guidelines require at least 24 weeks on ART before a child can be considered to have virological or immunological failure [21].

We defined the exposure as the period after a care interruption, starting on the date on which the child returns to care. We compared the mortality rate in the period before any care interruption (baseline group) to the mortality rate after a care interruption in those with a first care interruption within six months on ART (Group 1), and to the mortality rate after a care interruption in those with a first care interruption starting after six months on ART (Group 2). Person-years before the theoretical next visit date contribute time to the unexposed group, whilst person-years after the date of return to care contribute to one of the exposed groups, depending on whether the last visit date was within or after the first six months on ART. The time period between the theoretical next visit date and date of return to care (i.e. whilst the child is LTFU) is excluded, as mortality cannot be reliably ascertained during this period. In line with this, any known deaths whilst the child is LTFU are excluded, as the associated time

period is excluded. Children who never interrupt care contribute time to the baseline group, as they could have a care interruption in future.

Children known to have died but missing a date of death (n = 192) were assigned a date of death the day following their last clinic visit, in line with the approach adopted by Yotebieng et. al. [22]. Children LTFU who did not return to care are censored on the theoretical next visit date, 180 days after the last clinic date. Children who started ART <180 days before database closure or who died/transferred out <180 days after ART initiation were excluded as they could not meet the definition of experiencing a gap in care of >180 days before experiencing death/ transfer or database closure. In line with this, person-time for the first 6 months on ART is excluded. Figure 1b outlines the classification of person-time.

We calculated the time on ART before the first care interruption as the difference between the last visit date before the care interruption and the date of ART initiation.

Participants and exclusion criteria

This study includes all treatment-naïve, HIV-infected children initiating ART in the IeDEA-SA collaboration at age <16 years between 1 January 2004 and March 2016. Children entered the cohort the date they started ART, and exited on the earliest of date of death, date of transfer out or theoretical visit date if they hadn't visited the clinic for 180 days. Children re-entered the cohort if they returned to care. Children could therefore exit and re-enter the cohort multiple times, with active time in the clinic being included in person-time. Children with a baseline HIV-RNA measurement of <400 copies/ml were excluded, as it is unlikely they are treatment-naïve [22, 23]. Children that transferred in (defined as a first visit date >2 months after the ART initiation date) were excluded as information at ART initiation was often missing, and it was difficult to know if they had experienced a previous care interruption.

Statistical Analysis

We compared characteristics at ART initiation and characteristics of the time out of care using the Chi-square test for categorical variables, the t-test for normal quantitative variables, and the Wilcoxon rank sum test for non-normal quantitative variables. We assessed final outcomes (death, LTFU and remaining in care) using the Chi-square test.

We used Cox regression to evaluate the association between care interruptions starting within and after six months on ART and mortality, controlling for confounding variables. We considered the following possible confounders: gender, age, cohort, CD4% at ART initiation and calendar period of ART initiation. CD4% at ART initiation was the closest measurement to ART start date, within a window of six months before to one month after ART start. We used likelihood ratio tests to assess the overall contribution of each variable and potential effect modification. Time varying variables include the interruption group and age, with the timescale being time since first ART initiation.

Although we used 180 days out of care to define a care interruption, various definitions are used in literature. We therefore conducted a sensitivity analysis using different durations without a clinic visit to define care interruptions. We also conducted a sensitivity analysis varying the duration on ART before a care interruption which was used to classify the exposure (e.g. last visit before care interruption within three months after ART start). We conducted a further sensitivity analysis grouping those children lost immediately after ART initiation separately from those with a care interruption within six months but with at least one visit after ART start, given it is possible that children lost immediately after ART start did not start at all. A cohort analysis assesses the association in each individual cohort.

Statistical analysis was performed using STATA version 13 (STATA Corporation, College Station, TX).

Ethics

The IeDEA Southern Africa Collaboration has approval from the University of Cape Town and University of Bern Human Research Ethics Committees to collate anonymised routine individual patient data from HIV care and treatment programmes (approval number 084/2006). In addition, each site has local research ethics committee approval to participate in IeDEA-SA. The sites have received informed consent from patients if required by the respective research ethics committee, however for most sites this requirement has been waived as only routine anonymised data contributes to the dataset.

Results

The total cohort comprised 61,701 children, of whom 53,674 satisfied the inclusion criteria. Of these, 23,437 (44%) had at least one care interruption (Figure 2), with 10,629 (20%) having a care interruption within six months on ART and 12,808 (24%) having a care interruption after six months on ART.

Compared to children without a care interruption, those with a care interruption starting within six months on ART had a slightly higher CD4% at ART initiation (Table 1). In contrast, children with a care interruption after six months on ART were slightly older at ART initiation and more likely to have started ART before 2010 compared to children without a care interruption.

Children with a care interruption within six months on ART had longer first care interruptions (median duration 323 days vs. 244 days, p<0.001), and were out of care for an overall longer period of time (median duration 638 days vs. 467 days, p<0.001) than children who had a care interruption after six months on ART.

Overall, 23,315 (43%) of children were ultimately LTFU at the end of the study period. Children with a care interruption after six months on ART were less likely to be ultimately LTFU at the end of the study period than children without a care interruption and children

who had a care interruption within six months on ART (p-value <0.001). (Supplementary Table 2, http://links.lww.com/QAD/C456).

1,047 children died over the follow-up period (excluding those who died within the first 6 months on ART). 774 (74%) died without having had a care interruption, 161 (15%) died after having a first care interruption within six months on ART, and 112 (11%) died after having a first care interruption after six months on ART. Patients were followed up for a total of 141,359 person-years (mean 2.63 years, maximum 11.62 years), giving an overall rate of 7.41 deaths per 1000-person years (excluding the first 6 months and periods when the child was LTFU). A further 346 children are known to have died after meeting the definition of LTFU (Supplementary Table 2, http://links.lww.com/QAD/C456). These children are excluded from the analysis.

Univariable and multivariable analysis

In univariable analysis, a care interruption after six months of ART start was associated with a significantly lower risk of mortality (HR = 0.59, 95% CI 0.48 to 0.72), compared to no interruption. There was no evidence of an association between a care interruption within six months on ART and mortality (HR = 0.92, CI 0.77 to 1.09), compared to no interruption. (Table 2).

In multivariable analysis, a care interruption within six months of ART start was significantly associated with mortality, with an adjusted hazard ratio of 1.52 (95% CI 1.12 to 2.04), but there was no association between having a care interruption after six months on ART and mortality (AHR 1.05 (95% CI 0.77 to 1.44)).

Sensitivity Analysis

Sensitivity analysis showed that as the duration of care interruption increases in those with a care interruption within six months on ART, so the strength of association with mortality increases. (Supplementary Figure 1, http://links.lww.com/QAD/C456).

Analysis varying the duration on ART before the last visit showed that the association with mortality is greatest when a child has a care interruption where the last visit is within the first three months of initiating ART. Thereafter, the hazard ratio declines (Supplementary Figure 2, http://links.lww.com/QAD/C456).

Analysis separating out children with a care interruption directly after ART start showed that children with a care interruption within six months on ART but with at least one visit after ART start had an increased risk of mortality in line with the overall results (Supplementary Table 3, http://links.lww.com/QAD/C456).

The effect of a care interruption within six months of ART start was consistent across five cohorts; nine cohorts showed no significant association due to low overall mortality (Supplementary Figure 3, http://links.lww.com/QAD/C456).

Given a large proportion of children were missing CD4% at ART initiation, the adjusted analysis was re-run excluding CD4%, with a similar adjusted hazard ratio in both interruption groups (Care interruption within 6 months: AHR: 1.51 (95% CI 1.26 – 1.81); Care interruption after 6 months: AHR: 0.98 (95% CI 0.78 – 1.23) (Supplementary Table 4, http://links.lww.com/QAD/C456).

An analysis of the CD4% before and after the care interruption (Supplementary Table 5, http://links.lww.com/QAD/C456) showed an absence of a decline in disease severity during the care interruption, suggesting that children in this study may also continue taking their medications whilst out of care.

Discussion

Statement of principal findings

Care interruptions are important and need to be considered when assessing paediatric ART outcomes: among 53,674 children initiating ART, 44% had at least one care interruption. Having a care interruption within the first six months on ART is associated with increased mortality (AHR = 1.52, 95% CI 1.12 – 2.04), however there was no evidence of an association between having a care interruption after being on ART more than six months and mortality (AHR 1.05, 95% CI 0.77 - 1.44) . The effect of an increase in mortality following care interruptions was greatest in those who have a care interruption within three months of ART start, and declines thereafter. As the duration of the care interruption increases, so the strength of the association with mortality increases.

Comparison with other studies

This study supports the findings of other studies linking a treatment interruption (presumed break in ART) to negative HIV outcomes [7-10, 24]. In children starting ART due to clinical or immunological disease severity, mortality is highest in the first months after a child starts ART [25], therefore it is reasonable that there is a strong association between care interruptions in the first six months on ART. Nevertheless, we excluded children dying within the first six months on ART, and therefore the effect of high early mortality in sick children after ART start on the association between timing of the care interruption and mortality is likely minimised. Children with at least six months on ART will have had more time for their immune systems to recover, reducing their mortality risk [25].

Strengths and limitations of the study

Strengths include the prospective design and longitudinal nature of the study, the large number of participants and outcomes, a more representative sample of children attending HIV clinics through routine data, a large geographical area, and long follow-up period. An internal comparison group was used, minimising selection bias.

Several limitations should be considered. The use of routine data poses data quality issues. There is some missing data, the potential for inconsistencies in data collection from varying definitions and collection protocols across sites, and the potential for incorrect recording in baseline measurements, leading to residual confounding. Visit dates may have been omitted, leading to the child being incorrectly classified as LTFU. The final analysis excluded 50% of children owing to missing data in CD4% at ART initiation, which could give rise to selection bias. This could apply particularly to older children, when CD4 count is more likely to be used as an immunological marker instead of CD4%. Nonetheless, the results were similar when running the model without CD4, as noted in the results. (Supplementary Table 4, http://links.lww.com/QAD/C456).

There is potential for under-ascertained mortality through the high rate of ultimate LTFU (43%). Patients LTFU are likely to experience higher mortality than those that remain in care [26]. In our study, only deaths that occurred in care are taken into account. 1,047 children died whilst in care, however an additional 346 children are known to have died more than 6 months after their last visit, which have been excluded from the analysis.

A further limitation is that we cannot distinguish true ART interruptions (where the child stops taking ART) from interruptions in which children remains on ART, however does not attend clinic visits. A study in adults [14] found that that the majority of adults had a suppressed viral load upon resumption of care, indicating the patients had continued taking ART medications whilst out of care.

Information bias may arise through misclassification of the exposure. Potential misclassification of the exposure could occur owing to the use of a universal definition of LTFU (180 days) across all cohorts. 180 days may be too short for programs in which the time between clinic visits is longer, and too long for other sites. However, the cohort analysis revealed that results were consistent across five of the cohorts. 180 days may also be too short for the period just after ART initiation, as clinic visits may be more frequent in the initial period until the virus has been suppressed. The study may also be influenced by residual confounding and confounders not adjusted for, such as socioeconomic factors, parent HIV status, parent education, and disease status at the time of ART initiation. Due to using routine data, these factors were not measured.

Generalisability

The study included children from multiple clinics and countries across Southern Africa, reflecting a variety of care settings – a mix of urban and rural, ranging from small non-governmental organisation-led clinics to large government-run health systems [18] – and providing a wide mix of data allowing the findings to be generalisable across a variety of care settings. However, only IeDEA sites and clinics were included [18], and the children in this analysis may not represent all HIV-infected children on ART in the included geographic regions. LTFU is high, and the characteristic of children returning to care after becoming LTFU may be a regional sub-Saharan Africa phenomenon. One may be able to generalise to

other populations, however would need to consider the reasons why children are LTFU in each area, and social behaviours.

Conclusion

The results of the study support the hypothesis that a care interruption within the first six months on ART is associated with increased mortality. Given the high prevalence of care interruptions in the population, we need to increase efforts and interventions to retain children in care for the first six months after ART start. If resources for tracing and retention support are limited, efforts need to especially focus on those lost from care early where a care interruption is most strongly associated with mortality.

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Conflicts of interest and sources of funding

There are no conflicts of interest.

Authors' Contributions

All authors meet criteria for authorship. CD and MD contributed to the conception, design, and literature review. CD drafted the initial manuscript. MD, LJ, SS, CC, BE, MV, KT, JE, HR, SP, FT, KM, GF, MO, RW, SN and AH provided substantive edits to the manuscript. All authors have read and approved the final manuscript.

Additional files

Additional file 1: Supporting information

Pdf format. File contains all supplementary tables and figures.

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Figure 1a. Diagrammatic representation of a child's care trajectory b. Classification of person-time
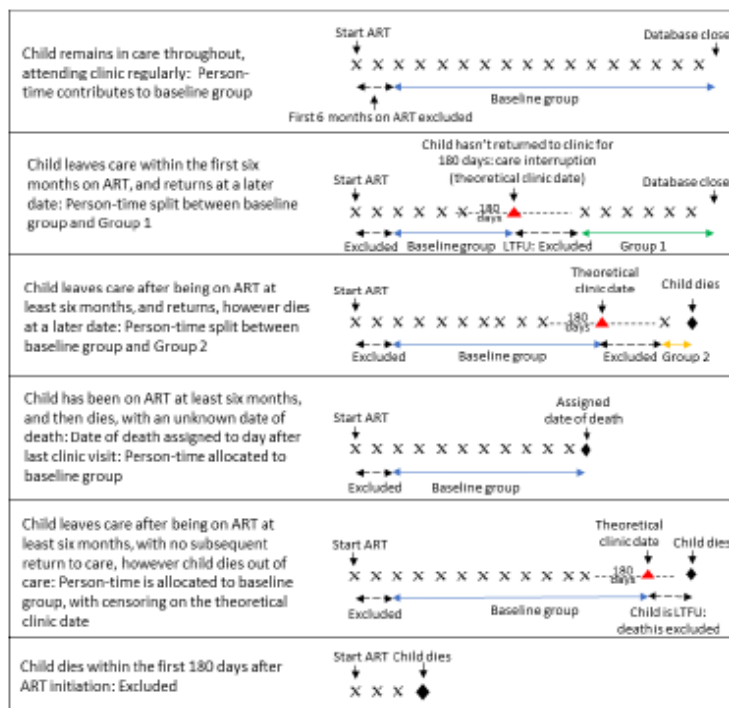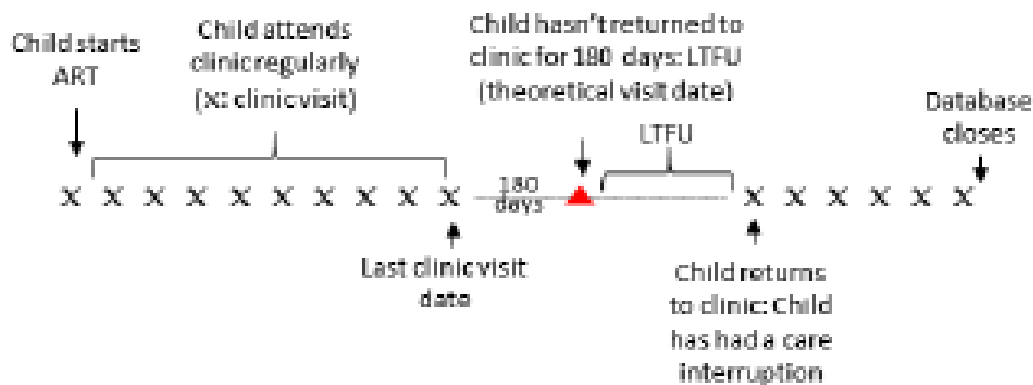
x: Each clinic visit is denoted with an 'x'

Figure 2. Flow diagram of the participants in the study

Children (<16) on ART between and 2004 and date of database closure (n = 61,701)

Baseline HIV-RNA measurement <400 copies/ml (n = 736)

Excluded from the analysis (n = 8,027)

Transferred in from other clinics (n = 1,773)

Children with less than 180 days of follow-up (n = 5,518)

Included in the analysis (r = 53,674)

Children without a care interruption (n = 30,237)

Children that experienced at least 1 care interruption (n = 23,437)

Retained in care throughout follow-up (n = 10,932)

Care Interruption within 6 months on ART (n = 10,629)

Died (r =161)

Died (n =774)

Care interruption after 6 months on ART (n =12,808)

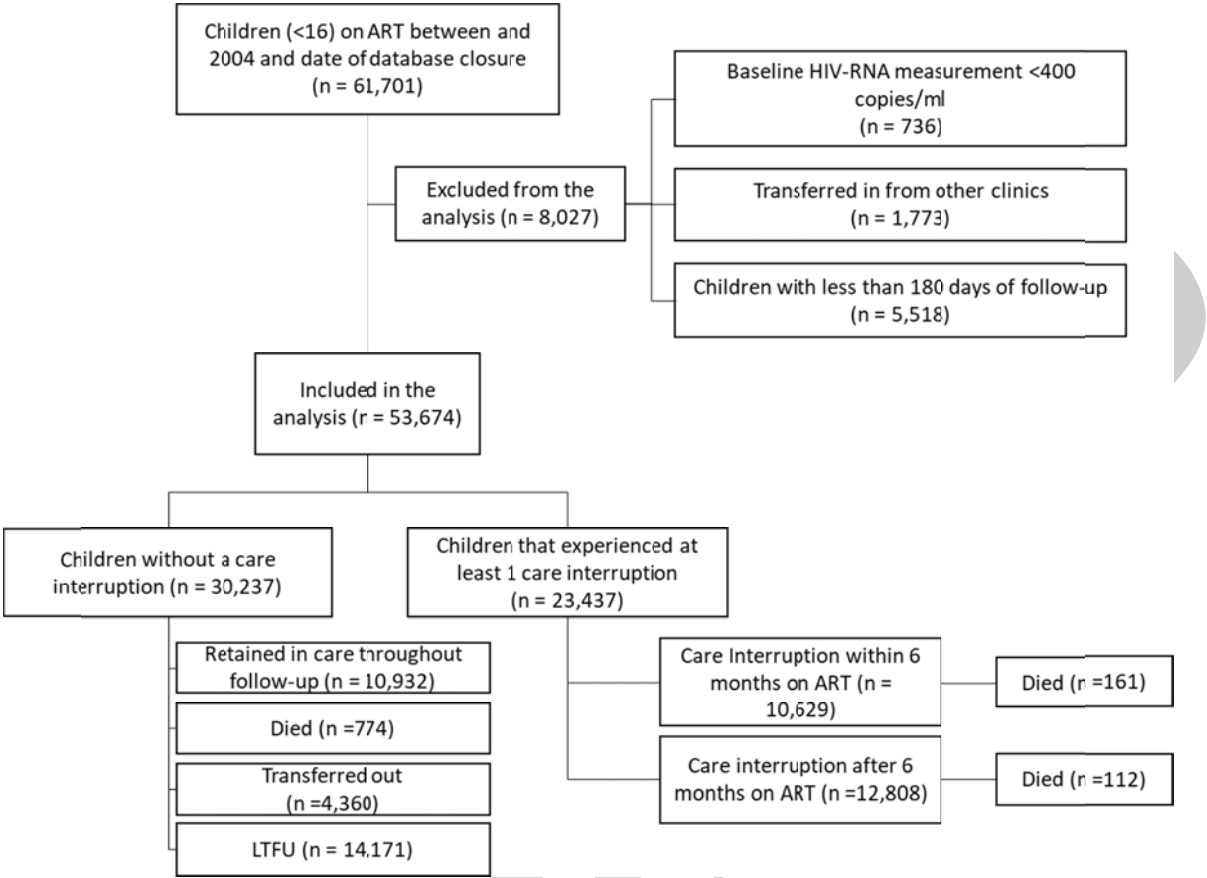Died (n =112)

Transferred out (n =4,360)

LTFU (n = 14,171)

Table 1. Characteristics at ART initiation of all children, stratified by care interruption

Characteristic	Total	Care Interruption status			p-value
		No Care Interruption	Care Interruption before 6 months	Care Interruption after 6 months	
	N	N (%)	N (%)	N (%)	
	(n = 53,674)	(n = 30,237)	(n = 10,629)	(n = 12,808)	
Gender					
Male	26,175	14,610 (48)	5,233 (49)	6,332 (49)	0.059
Female	27,499	15,627 (52)	5,396 (51)	6,476 (51)	
Age at ART initiation					
<2 years	13,128	7,945 (26)	2,674 (25)	2,509 (20)	<0.001
2-5 years	14,488	7,976 (26)	2,863 (27)	3,649 (28)	
6-9 years	12,555	6,774 (22)	2,466 (23)	3,315 (26)	
>=10 years	13,503	7,542 (25)	2,626 (25)	3,335 (26)	
Median (IQR) age at ART initiation	5.75 (2.05 - 10.03)	5.53 (1.88- 9.99)	5.71 (1.98 - 9.94)	6.26 (2.58 - 10.17)	
Year of ART initiation					
2004-2007	13,872	6,849 (23)	2,730 (26)	4,293 (34)	<0.001
2008-2009	11,450	6,000 (20)	1,789 (17)	3,661 (29)	
2010-2011	11,982	6,220 (21)	2,499 (24)	3,263 (25)	
2012-2016	16,370	11,168 (37)	3,611 (34)	1,591 (12)	
CD4 % at ART initiation					
<15%	12,873	6,734 (22)	1,919 (18)	4,220 (33)	<0.001
15-25%	8,505	4,416 (15)	1,529 (14)	2,560 (20)	
>=25%	5,375	2,720 (9)	1,102 (10)	1,553 (12)	
Missing	26,921	16,367 (54)	6,079 (57)	4,475 (35)	
Median (IQR) CD4% initiation	15.20 (9.74-22.80)	15.10 (9.50-22.67)	16.60 (10.90-24.50)	14.80 (9.30-22.00)	

IQR: Interquartile range. Column percentages are shown.

Table 2. Hazard ratio of the effect of a care interruption on mortality

Variable	Cases (n,%)	Person-years (1000's)	Mortality Rate per 1000 person-years	Unadjusted hazard ratio (95% CI)	Adjusted Hazard Ratio† (95% CI)	P-value
		(n=180.46)				
Care Interruption Status						
No Care Interruption	774	96.02	8.06 (7.51 - 8.65)	1.00	1.00	
Care Interruption before 6 months	161	21.67	7.43 (6.37 - 8.67)	0.92 (0.77 -1.09)	1.52 (1.12 - 2.04)	<0.001
Care Interruption after 6 months	112	23.67	4.73 (3.93 - 5.69)	0.59 (0.48 - 0.72)	1.05 (0.77 - 1.44)	
Gender						
Male	519	70.77	7.33 (6.73 - 7.99)	1.00	1.00	0.1910
Female	528	70.59	7.48 (6.87 - 8.15)	1.02 (0.90 - 1.15)	1.12 (0.95 - 1.33)	
Age						
<2 years	143	4.52	31.61 (26.83 - 37.24)	1.00	1.00	
2-5 years	242	32.60	7.42 (6.55 - 8.42)	0.24 (0.19 - 0.29)	0.27 (0.20 - 0.37)	<0.001
6-9 years	170	38.20	4.45 (3.83 - 5.17)	0.14 (0.11 - 0.18)	0.19 (0.13 - 0.26)	
>=10 years	492	66.04	7.45 (6.82 - 8.14)	0.24 (0.20 - 0.28)	0.29 (0.21 - 0.40)	
Year of ART initiation						
2004-2007	506	60.91	8.31 (7.61 - 9.06)	1.00	1.00	
2008-2009	267	36.80	7.25 (6.43 - 8.18)	0.87 (0.75 - 1.01)	0.68 (0.55 - 0.84)	<0.001
2010-2011	157	27.92	5.62 (4.81 - 6.58)	0.67 (0.56 - 0.80)	0.42 (0.32 - 0.55)	
2012-2016	117	15.73	7.44 (6.21 - 8.92)	0.88 (0.72 - 1.08)	0.29 (0.20 - 0.42)	
CD4 % at ART initiation						
<15%	350	41.12	8.51 (7.66 - 9.45)	1.00	1.00	
15-25%	131	23.02	5.69 (4.8 - 6.75)	0.67 (0.55 - 0.82)	0.63 (0.52 - 0.78)	<0.001
>=25%	57	13.10	4.35 (3.36 - 5.64)	0.51 (0.39 - 0.67)	0.45 (0.33 - 0.60)	

CI: Confidence Interval. †Results adjusted for all variables in the table, and cohort