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Mortality among adults transferred and lost to follow-up from antiretroviral therapy programmes in South Africa: a multicentre cohort study

Morna CORNELL¹, Richard LESSELLS^{2,3}, Matthew P. FOX^{4,5}, Daniela Belen GARONE⁶, Janet GIDDY⁷, Lukas FENNER^{8,9}, Landon MYER¹, and Andrew BOULLE¹ for the leDEA-Southern Africa collaboration

¹Centre for Infectious Disease Epidemiology & Research and Division of Epidemiology & Biostatistics, School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa ²Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Mtubatuba, South Africa ³Department of Clinical Research, London School of Hygiene and Tropical Medicine, United Kingdom ⁴Centre for Global Health & Development, Boston University, Boston, USA ⁵Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa ⁶Medecins Sans Frontieres, Cape Town, South Africa ⁷McCord Hospital, Durban, South Africa ⁸Institute of Social and Preventive Medicine, University of Bern, Switzerland ⁹Swiss Tropical and Public Health Institute, Basel, and University of Basel, Basel, Switzerland

Abstract

Background & objectives—Little is known about outcomes after transfer out (TFO) and loss to follow-up (LTF) and how differential outcomes might bias mortality estimates, as analyses generally censor or exclude TFOs/LTF. Using data linked to the National Population Register (NPR), we explored mortality among patients TFO and LTF compared with patients retained and investigated how linkage impacted on mortality estimates.

Methods—A cohort analysis of routine data on adults with civil-identification numbers starting ART 2004–2009 in four large South African ART cohorts. The number, proportion, timing and mortality of TFOs and LTF were reported. Mortality was compared using Kaplan-Meier curves, Cox's proportional hazards and competing risks regression.

Results—Before linkage, 1207 patients (6%) had died, 2624 (13%) were LTF, 1067 (5%) were TFO and 14583 (75%) were retained. Compared with retained, mortality risk was three times higher among TFOs (aHR 3.11, 95% CI 2.42–3.99) and 20 times higher among LTF patients (aHR 22.03, 95% CI 20.05–24.21). Excluding early deaths after TFO or LTF, the risk was comparable among TFOs and retained (aHR 0.75, 95% CI 0.54–1.03) and higher among LTF (aHR 2.85, 95%

Corresponding author & author for reprints: Morna CORNELL, School of Public Health & Family Medicine, Falmouth Building, Anzio Rd, Observatory 7925, South Africa. morna.cornell@uct.ac.za.

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CI 2.43–3.33). After linkage, corrected mortality was higher than site-reported mortality. Censoring did not however lead to substantial underestimation of mortality among TFOs.

Conclusions—While TFO and LTF predicted mortality, the lower incidence of TFO and subsequent death compared with LTF meant that censoring TFOs did not bias mortality estimates. Future cohort analyses should explicitly consider proportions TFO/LTF and mortality event rates.

Keywords

antiretroviral therapy; mortality; transfers; lost to follow-up

Introduction

Over the past 10 years, antiretroviral therapy (ART) programmes have undergone rapid expansion. There are now numerous large ART programmes in developing countries. As patient numbers increase, particularly in countries like South Africa with highly mobile populations, health systems will need to transfer patients efficiently to ensure uninterrupted linkage to care for optimal outcomes.

Although many programmes report the proportion of patients who are transferred out (TFO) to other services, little is known about how patients transition between services and their outcomes after TFO. Sites have limited capacity to keep track of large numbers of patients enrolled for ongoing care, while also continuing to increase enrolment onto ART[1], and accurate estimation of mortality within and outside ART programmes presents major challenges[2].

In recent years there has been a major focus on improving outcome ascertainment for patients who are lost to follow-up (LTF). Studies have documented increased mortality in LTF patients, especially within three months of being lost[3–5]. There have been attempts to standardise a definition of LTF in order to improve comparability across sites[6], and studies have utilised different methods in order to correct for unascertained deaths among patients LTF[4, 7–9]. In contrast with the growing body of literature on patients who are LTF, the group of patients who are TFO to another facility have received less attention. This is a significant group: in South Africa about 10% of patients who started ART over five years were TFO[10]. In addition, the probability of being TFO increased with each calendar year of ART initiation[11, 12]. Despite the scale of these losses, there is a dearth of information regarding patient outcomes after TFO, and the extent to which differential outcomes after TFO may bias mortality estimates on ART. Most analyses censor TFO patients' observations at the date of TFO[13–16], implicitly assuming that mortality after transfer is similar to mortality among patients retained, or exclude them from analysis[17].

Large and rapidly expanding ART programmes are unable to follow patients and confirm their vital status[18], and tracing studies are expensive and time-consuming. The International Epidemiologic Databases to Evaluate AIDS Southern African (IeDEA-SA) collaboration is uniquely placed to assess mortality after TFO/LTF. South Africa's vital registration system was estimated to capture 94% of deaths in the period 2007–2011. Many IeDEA-SA cohorts collect civil identification (ID) numbers, and using linkage to the

National Population Register (NPR), we can ascertain the vital status of patients with ID numbers after TFO/LTF.

In this study, we used data linked to the NPR to explore mortality among patients TFO and LTF compared with patients who were retained at the site of ART initiation. In addition, we investigated the extent to which the inclusion of deaths ascertained through linkage to the NPR for TFO and LTF patients impacted on mortality estimates compared to censoring at the time of TFO or LTF.

Ethics statement

All IeDEA-SA sites obtained ethical approval from relevant local institutions before contributing anonymised patient data to this collaborative analysis. In addition the collaboration has approval from the University of Cape Town Research Ethics Committee to receive and analyse these collaborative data.

Methods

This was a cohort analysis of routine data from four large South African adult IeDEA-SA sites which collect ID numbers: Hlabisa, a large rural programme encompassing 17 primary health care clinics; Khayelitsha, a primary care public sector clinic; McCord, a private/public urban hospital; and Themba Lethu, an urban public hospital. Treatment was free except in the McCord cohort, where patients paid a small co-payment. All ART-naïve HIV-positive adults (16 and 80 years) with ID numbers who started ART 2004–2009 were eligible for inclusion. The analysis was restricted to patients with ID numbers (65% overall) in order to ensure near-complete mortality ascertainment. Patients with and without ID numbers were compared to assess for potential selection bias.

Mortality was reported uncorrected (as recorded at site) and corrected (after linkage to the National Population Register). Once the data had been linked we checked whether patients had a date of death recorded. Patients whose date of death from the NPR preceded the date recorded for their outcome were recoded as dead, with the date from the NPR. TFO was defined by sites and was considered different from up-referral for treatment or down-referral for programmatic reasons. Generally patients were TFO at their own request for reasons of relocation, convenience or cost. A transfer letter and clinical summary were given to the patient along with sufficient ART to last until re-engaging in care. Patients were recorded as TFO and their status was updated in the database. There was no further follow-up. In Hlabisa, patients transferring between clinics within the sub-district were not regarded as TFOs. LTF was defined as no contact with the health facility for 6 months prior to analysis closure[2, 4] and not documented to be dead or TFO. Analysis was closed 6 months prior to database closure to allow time for this definition to be met for all individuals. The last contact date was taken as the date of LTF for those who met this definition.

Summary baseline characteristics (median, interquartile range (IQR) and proportions) were described by status (TFO, LTF and retained) for each cohort and overall. Differences between groups were tested with the chi-squared test (categorical variables) and the Wilcoxon rank-sum test (continuous). A sensitivity analysis was undertaken to compare

baseline characteristics of patients with and without IDs. The number, proportion, timing and mortality of patients TFO and LTF up to analysis closure were reported.

TFO and LTF were treated as time-varying covariates to avoid potential survivor bias in that these patients could not have died before TFO/LTF. All patients started in the retained group, with the date of ART initiation as the origin. Patients who were TFO/LTF contributed survival time to the retained group until the point at which they were transferred or lost, after which they contributed time to the relevant exposure category. Mortality was compared using Kaplan-Meier curves and Cox's proportional hazards regression. As there was high mortality directly after TFO/LTF, we undertook sensitivity analyses limited to, and then excluding, the first three months after TFO/LTF to ascertain whether there was a persistent difference in the risk of death. Three crude and multivariable models of associations between baseline characteristics, status (retained/lost to follow-up/transferred) and mortality are presented: Model 1 - overall period; Model 2 restricted to three months following the date of TFO/LTF; and Model 3 restricted to deaths beyond this period. Kaplan-Meier methods were used to estimate i) cumulative loss to programme; ii) mortality after TFO and LTF compared to retained patients, and iii) mortality after ART initiation in which patients previously classified as TFO or LTF were reclassified as having survived to analysis closure or having died based on NPR linkage. In addition, competing risks regression was used to estimate the cumulative incidence functions of death, LTF and TFO at 12 and 24 months after ART initiation. We assessed whether the effect of TFO on mortality risk was modified by the site of ART initiation (cohort) by including interaction terms in the models and testing with the F-test.

RESULTS

Overall 19507 eligible ART-naïve adults with ID numbers started ART during the study period (Figure 1). Of these, 26 (0.1%) were excluded due to: invalid dates (n=25) or unknown sex (n=1). The analysis included 19481 patients followed for 350463 person-months. The median duration of follow-up on ART was 15.5 person-months (IQR 5.7–27.5). At analysis closure, 1067 (5%) patients had been transferred out, 1207 (6%) had died, 2624 (13%) were LTF and 14583 (75%) were retained.

Patients who were retained were more likely to be female than those LTF (68 vs 61%, $p<0.001$, Table 1). Compared with those retained, the median CD4+ cell count was lower in those TFO and LTF (90 and 85 vs 109 cells/ μ L respectively, $p<0.001$), both overall (Table 1) and within each cohort (Table S1). At one and two years after ART initiation, the unadjusted cumulative incidence proportions were: death 5.5% (5.1–5.8) and 7.0% (6.6–7.4); LTF 9.8% (9.3–10.2) and 14.6% (14.1–15.2) and TFO 3.6% (3.3–3.9) and 6.0% (5.7–6.5) (Figure 2).

Overall 82 (8%) patients died after transfer date (Table 2). McCord transferred a far higher proportion of patients than the other sites (21% vs <6%) and had a higher proportion of deaths among TFOs (9% vs 6–8%). The majority of deaths after transfer took place during later ART (>3 months on ART), ranging from 77% (Khayelitsha) to 100% (Themba Lethu). Among transferred patients who died, the median time from ART to TFO was 3.9 months

(IQR 1.1–10.9 months), and was shorter in Khayelitsha and McCord hospital (<3 months) than in the other sites (7–8 months). The median baseline CD4+ cell count in patients who died was nearly half the median count in patients who survived (53 vs 94 cells/ μ L, $p=0.005$).

The proportions LTF varied by site: from 8% in Khayelitsha to 19% in Themba Lethu (Table 2). Mortality among LTF patients was 37% ($n=972$) (Table 2), ranging from 33–43% (Khayelitsha and McCord respectively). Mortality was high during later ART (51–71%). Among those who died during later ART, the majority of deaths occurred within three months of the LTF date, ranging from 58% (Themba Lethu) to 79% (Khayelitsha), $p<0.001$. The median time from ART enrolment to LTF in patients who died was 2.3 months. The median baseline CD4+ cell count in LTF patients who died was about half that of patients who survived (59 vs 104 cells/ μ L), $p<0.001$.

Transfer was predicted by CD4+ cell count and site of ART initiation (Table S3). In multivariable analysis, patients with a CD4+ cell count ≥ 200 cells/ μ L were less likely to be TFO than patients with a baseline count <25 cells/ μ L (aHR 0.74, 95% CI 0.60–0.91). McCord was five times as likely as Khayelitsha to transfer patients (aHR 5.24, 95% CI 4.27–6.42) and Hlabisa and Themba Lethu less likely (respectively aHR 0.74, 95% CI 0.60–0.91 and aHR 0.70, 95% CI 0.57–0.87) (Table S3). The effect of baseline CD4+ cell count on the likelihood of transfer was different in McCord from the other cohorts ($p=0.04$). Patients with higher baseline CD4 counts were less likely to be transferred except at McCord where CD4 count was not associated with risk of transfer.” TFOs increased cumulative programme loss by 24 months from 22% to 28% compared to accounting only for mortality and LTF (Figure 2a).

Figure 2b shows mortality with LTF and TFO treated as time-varying to remove potential survivor bias (presented separately by cohort in Figure S2). Patients TFO had higher mortality than patients retained. At 24 months on ART, 21% of the TFO patients compared with 8% of those retained had died. Patients who were LTF had extremely high early mortality. Twenty four months after starting ART, cumulatively 81% of LTF patients had died.

In crude analysis, mortality was associated with male gender, age, baseline CD4+ cell count, cohort and having been TFO or LTF (Table 3, Model 1). Men were more likely than women to die (HR 1.65, 95% CI 1.52–1.79). The risk of death increased with age and adults aged 45+ years compared with those 16–24 years had the highest mortality risk (HR 1.58, 95% CI 1.30–1.93). Mortality was inversely associated with baseline CD4+ cell count (HR 0.32, 95% CI 0.26–0.39, CD4+ cell count ≥ 200 vs 0–24 cells/ μ L). Compared with Khayelitsha, patients in McCord and Hlabisa had higher crude mortality risk (HR 2.26 and HR 1.48 respectively) and Themba Lethu patients had comparable risk (HR 1.06, 95% CI 0.94–1.22). In comparison with patients retained, the risk of death was higher for LTF patients (HR 20.2, 95% CI 18.5–22.05) and those TFO (HR 3.71, 95% CI 2.96–4.65).

In multivariable analysis of the total time period, adjustment for baseline characteristics, site of ART initiation and TFO/LTF status attenuated the association between mortality and male gender (aHR 1.19, 95% CI 1.09–1.31) and strengthened the association with age

(Table 3, Model 1). The impact of ART initiation site on mortality varied: the effect at Hlabisa and McCord was attenuated after controlling for the effect of LTF on mortality (Table S3, model 2), with little additional impact of controlling for the effect of TFO on mortality (Table S3, model 3). In Themba Lethu, adjustment for baseline characteristics reduced mortality estimates relative to other cohorts (aHR 0.59, 95% CI 0.51–0.69), with or without the inclusion of deaths amongst patients TFO or LTF. In sensitivity analyses, mortality was extremely high in the three-month period directly following LTF/TFO: aHR 32.21 (95% CI 29.18–35.56) and aHR 3.54 (95% CI 2.52–4.98) for LTF and TFO respectively compared with retained (Table 3 Model 2). Excluding deaths in the three months after TFO and LTF substantially changed mortality estimates for the effect of ART initiation site and TFO/LTF status (Table 3, Model 3). Compared with Khayelitsha, the effect of Hlabisa and McCord were strengthened and the effect of Themba Lethu was attenuated. Compared with patients retained, the risk among LTF was reduced from aHR 22.03 to aHR 2.85 (95% CI 2.43–3.33) and patients who were TFO had comparable mortality risk (aHR 0.75, 95% CI 0.54–1.03). In testing for interaction, Khayelitsha had higher mortality after TFO than the other cohorts, consistent with Figure S1. However, the impact of these additional deaths on mortality in the cohort was negligible (Figure S2).

Figure 2c shows the impact of correcting mortality estimates via NPR linkage). In all cohorts, crude (site-reported) mortality substantially underestimated mortality. Correction for deaths among patient LTF substantially increased mortality estimates, while additionally accounting for unascertained deaths in the smaller proportion of patients TFO had a limited effect on overall cumulative mortality estimates.

DISCUSSION

In this analysis of 19481 ART-naïve adults with civil identification numbers starting ART between 2004 and 2009, patients who were transferred had higher mortality than patients retained at the ART initiation site. Mortality among TFOs was low, with one third occurring in the three-month period directly after TFO. Mortality after LTF was far higher, particularly during early ART and in the period directly after LTF. Excluding the mortality directly after TFO/LTF, the mortality risk among patients TFO and retained was similar, but patients LTF had three times the mortality risk of those retained. After linkage to the NPR, correction for deaths among patients TFO had limited impact on mortality but correction for LTF substantially increased mortality estimates. The inclusion of deaths after LTF, but not those after TFO, changed the association between treatment cohort and mortality.

The South African ART programme has undergone rapid expansion since its inception in 2004. In 2009/10, a total of 550 accredited facilities were established to offer ART[19]. By 2012, 3686 facilities (80% of the total) offered ART[20]. This expansion in facilities offering ART has provided more opportunity for TFOs within the health system. Indeed the probability of TFO at one year increased from 1.4% in patients enrolled 2002–2004 to 8.9% in patients enrolled in 2009[12]. Lowering the threshold of ART eligibility is likely to increase patient numbers further [11] and may mean that more mobile individuals are enrolled on ART. In addition, evidence suggests that even in low-income countries, patients actively seek better quality health care despite higher costs if they believe that this may

improve their outcomes[21]. There is thus a need for a robust system in order to ensure that patients who are TFO successfully re-engage in care in another facility without increased risk of mortality. Our study highlighted a number of issues related to patient transfers which have programmatic implications.

Firstly, over a third of deaths in those TFO during later ART occurred in the three month period directly after TFO. It is plausible that patients may have been requesting transfer at a time of severe illness in order to be cared for at home or in the expectation of death[22], or may have been actively transferred to better equipped services due to illness. South Africa has a long history of circular labour migration. Individuals leave home to find work in urban areas and return home to receive care and to die in rural areas where their families remain[23]. Our findings suggest the need for close monitoring after TFO to ensure that TFO patients have successfully linked to care, and for the rapid recall of lost patients.

Second, patients who were transferred had comparable or lower mortality than those retained beyond the three months following transfer (aHR 0.75, 95% CI 0.54–1.03, Table 3, Model 2). This is important new information on a group of patients whose outcomes have been largely unknown. Our finding differs from a Malawi study which reported improved survival among TFOs compared with patients retained over 24 months (5% vs 12%)[24]. Our results suggest that once patients have stabilised on treatment, TFO may not impact on mortality, or that beyond the early months on ART stable patients are more likely than others to be transferred. Indeed, in Malawi, patients who were transferred had less advanced clinical stage of disease and better survival than those retained.

Third, some transfers may have been due to resource constraints among patients battling to access health care. For example, McCord Hospital transferred a far larger proportion of patients, and experienced far higher mortality after TFO. In this cohort, patients were required to make a small co-payment towards their treatment. The co-payment covered all HIV-related out-patient care for the month, with no additional costs for any investigation or treatment, but did not cover in-patient admission care. Previous research has found free provision of ART associated with lower mortality in low-income countries[25]. It is plausible that patients requesting transfer in this cohort were unable to afford even the small co-payment, which increased from R120 per consultation in 2005 to R140 in 2008.

Fourth, our study confirms the major threat that LTF poses to programme effectiveness [4, 10, 26–29]. Almost half of the LTF patients had died, mostly within three months of being LTF. The timing of deaths was similar to deaths after TFO, but mortality was far higher. Even excluding the three month period directly after LTF, LTF patients still had nearly three times the risk of death compared with retained patients (AHR 2.85, 95% CI 2.43–3.33). Retention in chronic HIV care has long been recognised as a major challenge [10, 13, 28, 30, 31], with LTF increasing by calendar year as ART programmes scale-up enrolment [10, 20, 31]. Numerous strategies have been proposed to retain patients in care include decentralising ART provision and taskshifting[32], reducing clinic caseloads[33] and managing ART at community-[34] and home-level[35]. Urgent attention is needed to prevent LTF particularly in the first few months on ART.

Finally, although in all cohorts the median CD4+ cell count at ART initiation was lower among TFOs and LTF than those retained, there was substantial heterogeneity across sites including in the proportions TFO/LTF, the incidence of mortality, the median time from ART initiation to TFO/LTF in patients who died, and the median baseline CD4+ cell count in patients who died compared with those who survived. Such variability suggests that although TFO is reported as a single outcome, it may have different meanings in different sites which may impact on mortality. Sites need to understand what TFO means in their own context.

In addition to the implications for patient care, our analysis has implications in terms of programme evaluation. Accurate ascertainment of mortality poses major challenges, particularly in large programmes in developing countries with limited capacity to actively follow patients. In the absence of additional outcome ascertainment, many studies censor the follow-up time of patients who are TFO, assuming that mortality is the same as among patients retained. Using linkage, our study provides evidence that in a context of low TFO rates and mortality rates after TFO, censoring follow-up time at TFO date did not lead to a substantial underestimation of mortality. In contrast, including deaths among LTF compared with censoring at the time of LTF impacted on mortality estimates and the effect of baseline characteristics as well as cohort on mortality. Thus if the proportion transferred and the event rates were higher, it might be necessary analytically to treat TFO in a similar way to LTF. In situations where additional outcome information is available from, for example, tracing studies or linkage to a population register, statistical methods such as inverse probability weighting and/or multiple imputation can be used [36]. In the absence of such information, options include the use of a nomogram to correct mortality estimates[7] and use of selection and pattern-mixture models[37].

So what are the implications of our findings, particularly in the context of policy initiatives to test and treat all people with HIV? The study highlights the need for improved follow-up especially in the months after TFO and LTF. South Africa has a number of factors which should support good patient follow-up. ART is widely available; by 2013, approximately 80% of all primary health care facilities were offering ART services and this number appears set to increase[38]. In addition, there are standardised ART guidelines which are widely disseminated, ensuring a fairly unified approach to treatment across facilities and providers. These guidelines could be substantially strengthened by a standardised approach to transferring and following patients, with a particular focus on the timing of patients transferred. We recommend: 1) extreme caution in transferring patients until they are clinically stable on ART; 2) prompt and comprehensive reassessment at the receiving facility to ensure continuity of care, not only in terms of ART but also for co-morbid conditions, particularly in the three-month period directly after TFO/LTF; 3) prompt follow-up of patients who are LTF; and 4) a single patient identifier for all health facilities and much improved national health information systems to support monitoring and evaluation.

To our knowledge, this is the first study to report mortality among patients TFO, using data from linkage to the NPR. Most analyses from large ART programmes underestimate mortality due to high LTF and poor vital registration. This study was strengthened by our ability to explore the vital status of patients after leaving a programme, which would

generally only be possible by undertaking expensive tracing studies with limited success. The analysis only included patients with ID numbers, ensuring good mortality ascertainment. A limitation is that patients with ID numbers may have been different from those without ID which may have led to some underestimation of the true mortality after TF. However in sensitivity analysis, there was no evidence of any substantial differences between those with and those without IDs (Table S5). A further limitation is the possible misclassification of outcomes. Patients classified as LTF may be silent TFOs, while some patients LTF may be incorrectly classified as TFO. In addition, different reasons for patient transfer may independently impact on mortality risk but cohorts did not capture patients' reasons for TFO. Finally, due to the observational nature of the study, we were unable to determine whether the increased risk of mortality in those transferred was causally related to the transfer itself or was related to unmeasured characteristics of the individuals transferred, or information bias due to misclassification

In summary, improved administrative and clinical procedures to ensure continuity and quality of care for patients TFO and LTF are needed. As the proportion of patients TFO increases, it will become increasingly important in cohort analyses to consider the potential for differential outcomes in TFO patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Flowchart of 19507 ART-naïve adults with civil identification numbers initiating ART 2004–2009

Figure 2a Cumulative proportion of patients lost, by method of loss

Figure 2b. Mortality among patients transferred, LTF and retained

Figure 2.

Figure 2a: Cumulative proportion of patients lost to programme by method of loss

Figure 2b: Mortality among patients transferred and lost to follow-up compared with patients retained

Figure 2c: The impact on mortality estimates of correction via the National Population Register

Table 1

Baseline characteristics of patients by outcome status (transferred/lost to follow-up/retained) in four South African cohorts of IeDEA-SA (n=19481)

Baseline characteristic	TFO n=1067 (5%)	LTF n=2624 (13%)	Retained n=14583 (75%)	TOTAL n=19,481 (100%)	p-value TFO vs retained	p-value LTF vs retained
Gender						
Females, n(%)	744 (70)	1613 (61)	9939 (68)	12992 (67)	0.286	<0.001
Age, years, median (IQR)	34 (29–41)	34 (29–41)	34 (29–41)	35 (30–42)	<0.001	<0.001
CD4+ cell count, cells/ μ L						
Median (IQR)	90 (39–152)	85 (35–155)	109 (51–168)	103 (44–164)	<0.001	<0.001
0–24 n(%)	160 (15)	453 (17)	1791 (12)	2718 (14)		
25–49	127 (12)	316 (12)	1433 (10)	2071 (11)		
50–99	223 (21)	511 (19)	2803 (19)	3771 (19)		
100–199	362 (34)	818 (31)	5782 (40)	7236 (37)		
>=200	67 (6)	223 (9)	1378 (9)	1743 (9)		
missing, n(%)	128 (12)	303 (12)	1396 (10)	1948 (10)		
Haemoglobin, g/dL						
Median (IQR)	11 (9.6–12.1)	11 (9.2–12.1)	11.1 (10–12.6)	11 (9.8–12.4)	<0.001	<0.001
missing (%)	26%	21%	18%	19%		
Weight, kg						
Median (IQR)	58 (51–66)	58 (50–66)	60 (53–68)	59 (52–68)	<0.001	<0.001
missing (%)	24%	18%	13%	14%		
Calendar year ART initiation, n(%)						
2004	205 (19)	342 (13)	1303 (9)	1990 (10)	<0.001	<0.001
2005	312 (29)	639 (24)	2381 (16)	3613 (19)		
2006	261 (25)	607 (23)	3283 (23)	4447 (23)		
2007	145 (14)	489 (19)	3199 (22)	4128 (21)		
2008	120 (11)	389 (15)	2804 (19)	3461 (18)		
2009	24 (2)	158 (6)	1613 (11)	1848 (9)		

* including 1207 (6%) patients dead at analysis closure

Table 2

Number (%), timing and mortality* of patients transferred and lost to follow-up

	Total n=19481	Hlabisa n=8208	Khayelitsha n=3397	McCord n=1641	Themba Lethu n=6235	p-value*
<i>Patients transferred out (TFO), n(%)</i>	1067 (5)	287 (3)	161 (5)	349 (21)	270 (4)	<0.001
Deaths after transfer date	82 (8)	21 (7)	13 (8)	31 (9)	17 (6)	<0.001
Deaths during early ART (0–3 months)	7 (9)	2 (10)	3 (23)	2 (6)	0 (0)	0.026
Deaths during later ART (> 3months)	75 (91)	19 (90)	10 (77)	29 (94)	17 (100)	0.721
Among deaths during later ART, deaths <3 months after TFO	27 (36)	8 (42)	6 (60)	5 (17)	8 (47)	0.151
Median months from ART start to transfer	9.4 (3.7–19.2)	9.0 (3.5–18.9)	7.7 (3.4–16.3)	9.2 (3.7–19.4)	11.1 (4.1–20.2)	
Median months from ART start to TFO in patients who died	3.9 (1.1–10.9)	6.9 (2.8–11.9)	2.3 (0.4–6.0)	2.8 (0.9–6.5)	8.2 (3.0–14.6)	
Median months from TFO to death	3.8 (1.1–12.3)	3.1 (1.0–6.9)	1.1 (0.6–3.2)	7.8 (3.1–15.5)	5.1 (0.9–17.6)	
Median months from ART to death	11.9 (5.1–19.8)	13.0 (6.1–17.3)	5.0 (3.6–9.9)	12.5 (8.5–21.4)	19.7 (7.0–25.2)	
Median baseline CD4+ cell count in patients who died	53 (14–121)	90 (11–162)	40 (17–99)	41 (12–90)	77 (14–121)	0.005**
Median baseline CD4+ cell count in patients who survived	94 (41–153)	116 (53–167)	88 (38–134)	92 (42–158)	79 (30–137)	
<i>Patients lost to follow-up (LTF), n(%)</i>	2624 (13)	921 (11)	281 (8)	265 (16)	1157 (19)	<0.001
Deaths after LTF	972 (37)	380 (41)	94 (33)	114 (43)	384 (33)	<0.001
Deaths during early ART (0–3 months)	379 (39)	170 (45)	46 (49)	52 (46)	111 (29)	<0.001
Deaths during later ART (> 3 months)	593 (61)	210 (55)	48 (51)	62 (54)	273 (71)	0.105
Among deaths during later ART, deaths <3 months after LTF	379 (64)	147 (70)	38 (79)	37 (60)	157 (58)	<0.001
Median months from ART start to LTF	6.7 (1.1–17.0)	6.4 (0.9–16.2)	7.6 (1.8–17.6)	4.7 (0.9–12.1)	7.4 (1.4–18.0)	
Median months from ART to LTF in patients who died	2.3 (0.4–8.3)	1.8 (0.0–8.6)	1.9 (0.5–6.3)	1.8 (0.5–6.5)	3.0 (0.5–9.0)	
Median months from LTF to death	0.8 (0.3–2.4)	0.8 (0.3–1.8)	0.4 (0.2–1.2)	0.6 (0.2–1.8)	1.1 (0.5–4.4)	
Median months from ART to death	5.0 (1.5–13.2)	4.0 (1.2–12.1)	3.1 (1.0–9.7)	3.3 (1.1–10.5)	6.9 (2.5–16.1)	
Median baseline CD4+ cell count in LTF patients who died	59 (19–121)	69 (24–136)	65 (34–122)	40 (11–88)	52 (15–110)	<0.001**
Median baseline CD4+ cell count in LTF patients who survived	104 (48–168)	117 (60–177)	113 (57–169)	79 (36–114)	98 (42–163)	

Table 3

Associations with mortality, with time-varying status (retained/lost to follow-up/transferred)

Model 1 Total time period		Model 2 3 months after TFO/LTF		Model 3 Excluding 3 months after TFO/LTF	
Crude HR	AHR	Crude HR	AHR	Crude HR	AHR
1.65 (1.52–1.79)	1.19 (1.09–1.31)	1.67 (1.53–1.83)	1.21 (1.10–1.33)	1.56 (1.41–1.73)	1.27 (1.14–1.42)
1	1	1	1	1	1
1.13 (0.94–1.36)	1.29 (1.05–1.57)	1.11 (0.92–1.35)	1.23 (0.99–1.52)	1.11 (0.88–1.39)	1.14 (0.89–1.46)
1.28 (1.06–1.54)	1.48 (1.20–1.82)	1.24 (1.02–1.52)	1.35 (1.09–1.68)	1.22 (0.97–1.54)	1.22 (0.95–1.57)
1.58 (1.30–1.93)	1.99 (1.61–2.47)	1.60 (1.30–1.96)	1.85 (1.48–2.32)	1.52 (1.19–1.93)	1.58 (1.22–2.05)
1	1	1	1	1	1
0.77 (0.68–0.88)	0.72 (0.63–0.82)	0.76 (0.66–0.87)	0.70 (0.61–0.81)	0.82 (0.69–0.96)	0.78 (0.66–0.92)
0.52 (0.46–0.58)	0.50 (0.44–0.57)	0.50 (0.44–0.57)	0.48 (0.42–0.55)	0.53 (0.46–0.62)	0.51 (0.44–0.60)
0.32 (0.29–0.36)	0.33 (0.29–0.37)	0.30 (0.27–0.34)	0.32 (0.28–0.36)	0.33 (0.29–0.38)	0.31 (0.27–0.36)
0.32 (0.26–0.39)	0.29 (0.24–0.36)	0.30 (0.25–0.38)	0.29 (0.24–0.36)	0.36 (0.29–0.46)	0.33 (0.26–0.42)
1	1	1	1	1	1
1.48 (1.30–1.69)	1.27 (1.10–1.46)	1.46 (1.28–1.68)	1.27 (1.09–1.47)	1.54 (1.31–1.80)	1.48 (1.25–1.75)
2.26 (1.92–2.66)	1.21 (1.01–1.46)	2.13 (1.79–2.53)	1.25 (1.03–1.51)	2.8 (2.20–3.27)	1.92 (1.54–2.39)
1.06 (0.94–1.22)	0.59 (0.51–0.69)	0.96 (0.83–1.11)	0.61 (0.52–0.71)	0.96 (0.81–1.15)	0.74 (0.61–0.89)
1	1	1	1	1	1
20.20 (18.50–22.05)	22.03 (20.05–24.21)	31.59 (28.83–34.63)	32.21 (29.18–35.56)	2.38 (2.06–2.76)	2.85 (2.43–3.33)
3.71 (2.96–4.65)	3.11 (2.42–3.99)	3.54 (2.52–4.98)	3.03 (2.09–4.40)	0.93 (0.69–1.24)	0.75 (0.54–1.03)