Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002–2007

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Objective: Little is known about the temporal impact of the rapid scale-up of large antiretroviral therapy (ART) services on programme outcomes. We describe patient outcomes [mortality, loss-to-follow-up (LTFU) and retention] over time in a network of South African ART cohorts.

Design: Cohort analysis utilizing routinely collected patient data.

Methods: Analysis included adults initiating ART in eight public sector programmes across South Africa, 2002–2007. Follow-up was censored at the end of 2008. Kaplan–Meier methods were used to estimate time to outcomes, and proportional hazards models to examine independent predictors of outcomes.

Results: Enrolment ($n = 44\,177$, mean age 35 years; 68% women) increased 12-fold over 5 years, with 63% of patients enrolled in the past 2 years. Twelve-month mortality decreased from 9% to 6% over 5 years. Twelve-month LTFU increased annually from 1% (2002/2003) to 13% (2006). Cumulative LTFU increased with follow-up from 14% at 12 months to 29% at 36 months. With each additional year on ART, failure to retain participants was increasingly attributable to LTFU compared with recorded mortality. At 12 and 36 months, respectively, 80 and 64% of patients were retained.

Conclusion: Numbers on ART have increased rapidly in South Africa, but the programme has experienced deteriorating patient retention over time, particularly due to apparent LTFU. This may represent true loss to care, but may also reflect administrative error and lack of capacity to monitor movements in and out of care. New strategies are needed for South Africa and other low-income and middle-income countries to improve monitoring of outcomes and maximize retention in care with increasing programme size.

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Introduction

South Africa has the largest antiretroviral therapy (ART) programme in the world [1]. Between 2004 (the start of the national ART programme) and 2007, an estimated 370 000 people initiated treatment in the public sector [2]. But, despite the scope and rapid growth of this programme there are no data on programme outcomes at a national level. The International Epidemiologic Databases to Evaluate AIDS collaboration of Southern Africa (IeDEA-SA) has assembled a series of HIV treatment cohorts from across the country that include approximately 10% of all adults who initiated public sector ART in South Africa by the end of 2007. The aim of this paper is to describe trends in mortality, loss-to-follow-up (LTFU) and programme retention of these adult patients over the first 5 years of the country's national ART programme.

Methods

Study design, population and eligibility criteria

The South African cohorts of IeDEA-SA have been described in detail elsewhere [3]. Briefly, the collaboration includes eight adult cohorts providing ambulatory ART services located in the four largest provinces in the country (Western Cape, Free State, Gauteng and Kwazulu-Natal). This analysis included all HIV-positive adults (≥16 years) who initiated ART in these cohorts between 2002 and 2007.

Variables and definitions

Baseline characteristics included demographics (age, sex), available measures of disease severity (CD4 cell count, WHO stage and viral load) and calendar year of ART initiation. Outcome measures were mortality, LTFU and programme retention. Deaths and transfers were defined by active or passive follow-up at site level. Patients were defined as LTFU if their last patient contact was more than 6 months before the date of closure of the cohort database and were censored at their last contact date. Patients who were transferred out were censored at the transfer date. For patients who started ART but had no further contact with the clinic, 1 day of follow-up was added to allow their inclusion in survival analyses. Programme retention was defined as those who were enrolled and not dead or LTFU at analysis closure.

Person-time in the database included patients commencing ART from January 2002 until December 2007. Database closure was on or before 31 December 2008 (with minor variation across cohorts).

Analysis

Baseline characteristics were described with summary statistics (medians, interquartile ranges and proportions). Because of variability in the completeness of baseline data, patient numbers are reported for each analysis. Mean age, median CD4 cell count and proportion in WHO Stage IV were calculated by year of enrolment. Temporal trends were tested with the nonparametric test for trend across continuous variables (age and CD4 cell count). Differences between proportions were tested with the chi-square test. Time to death, LTFU and overall programme retention were analysed using Kaplan–Meier methods and presented by year of enrolment.

Separate proportional hazards regression models, stratified by cohort, were used to assess crude and adjusted associations between patient characteristics and different outcomes. We modelled the proportional hazards of death separately for different time periods as the risk factors for

Table 1. Patient characteristics at ART initiation[a].

Characteristic	Adults (≥16 years) $n = 44\,177$
Sex, *n* (%)	44 177 (100)
Women, *n* (%)	29 904 (67.7)
Age, *n* (%)	44 177 (100)
Adults (years), median (IQR)	35.0 (29.9–41.6)
Age categories, *n* (%)	
16–24	2306 (5.2)
25–34	17 654 (40.0)
35–44	16 177 (36.6)
45+	8040 (18.2)
Year of initiation, *n* (%)	44 177 (100)
2002/2003	1173 (2.7)
2004	5262 (11.9)
2005	9909 (22.4)
2006	13 105 (29.7)
2007	14 728 (33.3)
Absolute CD4 cell count (cell/μl), *n* (%)	36 549 (82.7)
All adults, median (IQR)	103 (45–164)
CD4 cell count, categorical, *n* (%)	
<50	9947 (27.2)
50–199	22 703 (62.1)
≥200	3899 (10.7)
HIV RNA level, $\log_{10}$ copies/ml, *n* (%)	18 684 (42.3)
Median (IQR)	4.9 (4.4–5.4)
RNA level, categorical, *n* (%)	
≤5 Log	10 405 (55.7)
>5 Log	8279 (44.3)
WHO stage, *n* (%)	11 393 (25.8)
I	979 (8.6)
II	1335 (11.7)
III	5463 (48.0)
IV	3616 (31.7)

[a]With number of patients with available data for each characteristic.

death vary, particularly during the first year on ART [4,5]. The proportional hazards assumption was confirmed using Schoenfeld and scaled Schoenfeld residuals. Models were built by adding relevant variables with progressively less complete data, to preserve as many observations as possible. Data on WHO staging, an important predictive variable, were missing for 74% of patients. Consequently, we present two final models (including and excluding WHO stage) for each time period. We report findings from the models excluding WHO stage, and where WHO staging impacted appreciably on results, we report this.

Although the national ART rollout programme started on 1 April 2004, we included a small proportion of adults who had received ART through donor-funded programmes prior to this date. There were no differences in baseline characteristics between patients started in 2002/2003 and those started in 2004, and in a sensitivity analysis (not shown) no aspect of the study findings was substantively different when patients starting ART in 2002/2003 were excluded.

Data were analysed using STATA 11.0 (STATA Corporation, College Station, Texas, USA). Two-sided statistical tests were used at $\alpha = 0.05$. All IeDEA-SA sites obtained ethical approval from relevant local institutions before contributing anonymized patient data to this collaborative analysis.

Results

Patient characteristics

This analysis included 44 177 adults who started ART between 2002 and end of 2007 (median age 35 years; 68% women, Table 1), contributing a total of 66 434 person-years of follow-up [median 1.27 years, interquartile range (IQR) 0.64–2.20]. Among those with CD4 cell counts at baseline (83%, $n = 36\,549$), median CD4 cell count was 103 cells/μl (IQR 45–164), and 27% had a CD4 cell count below 50 cells/μl. The median baseline log viral load measures (available for 18 684 participants, 42%), was 4.9 copies/ml (IQR 4.4–5.4). A total of 11 393 (26%) patients had baseline staging, and 80% of these ($n = 9079$) were classified as WHO stage III/IV.

Temporal changes in patient characteristics and outcomes

Enrolment increased each calendar year, from 1173 in 2002/2003 to 14 728 in 2007 (Table 2). The majority of patients were enrolled in the past 2 years of the period under analysis (63%, $n = 27\,833$). With each successive year of the programme, patients were enrolled at older ages and with less advanced HIV disease. Mean age increased from 34 years in 2002/2003 to 37 years in 2007 ($P < 0.001$). Median CD4 cell count increased from 68 cells/μl in 2002/2003 to 113 in 2007 ($P < 0.001$). Over the same period, among patients with baseline WHO staging, the proportion of patients with Stage IV disease decreased from 50 to 28% ($P < 0.001$).

Between 2002/2003 and 2006, 12-month reported mortality declined from 9 to 6% ($P < 0.001$) (Table 2, Fig. 1a). Meanwhile 12-month LTFU increased with each calendar year of enrolment, from 1% in 2002/2003 to 13% in 2006 ($P < 0.001$), and 12-month programme retention declined from 90 to 82% over the same period ($P < 0.001$) (Table 2). The crude effect of calendar year persisted over 5 years of follow-up (Fig. 1a–c).

LTFU increased with duration on treatment (Table 3, Fig. 1b) and made an increasing contribution to overall patient attrition. At 6 months on ART, one-third of the losses to programme were due to mortality: 5% of patients had died while 9% were LTFU. By 36 months, mortality accounted for one-quarter of patient losses: 10% were dead and 30% were LTFU. Overall programme retention dropped from 86% at 6 months to 71% at 24 months and 64% at 36 months.

Associations with baseline characteristics

In all time periods, there was a slight increase in the crude and adjusted risk of death for older patients [adjusted hazard ratio (HR) 1.03, 95% confidence interval (CI) 1.02–1.04, Table 4, 12–36 months]. There was a strong association between year of enrolment and the risk of death on ART. With each successive year of enrolment the risk of mortality decreased. The risk of death in the

Table 2. Baseline characteristics and 12-month outcomes by calendar year of ART initiation.

	Year of enrolment				
	2002/2003	2004	2005	2006	2007
Age, mean (95% CI)	34.3 (33.9–34.8)	35.7 (35.4–35.9)	35.7 (35.6–35.9)	36.2 (36.0–36.3)	36.9 (36.8–37.1)
CD4, median (IQR) ($n = 36\,549$)	68 (23–130)	87 (38–147)	102 (44–160)	106 (46–168)	113 (51–170)
Patients in Stage IV, *n* (%) ($n = 11\,393$)	434 (50.2)	708 (38.5)	998 (31.3)	998 (26.5)	478 (27.7)
12-month mortality % (95% CI)	8.9 (7.4–10.7)	7.2 (6.5–7.9)	7.4 (6.9–7.9)	6.2 (5.8–6.7)	5.6 (5.1–6.0)
12-month LTFU % (95% CI)	1.1 (0.6–1.9)	8.6 (7.9–9.4)	10.3 (9.7–10.9)	13.1 (12.5–13.7)	23.5 (22.7–24.3)
12-month retention % (95% CI)	90.1 (88.2–91.7)	84.8 (83.8–85.8)	83.1 (82.3–83.8)	81.5 (80.8–82.1)	72.3 (71.4–73.1)

CI, confidence interval; IQR, interquartile range; LTFU, lost to follow-up.

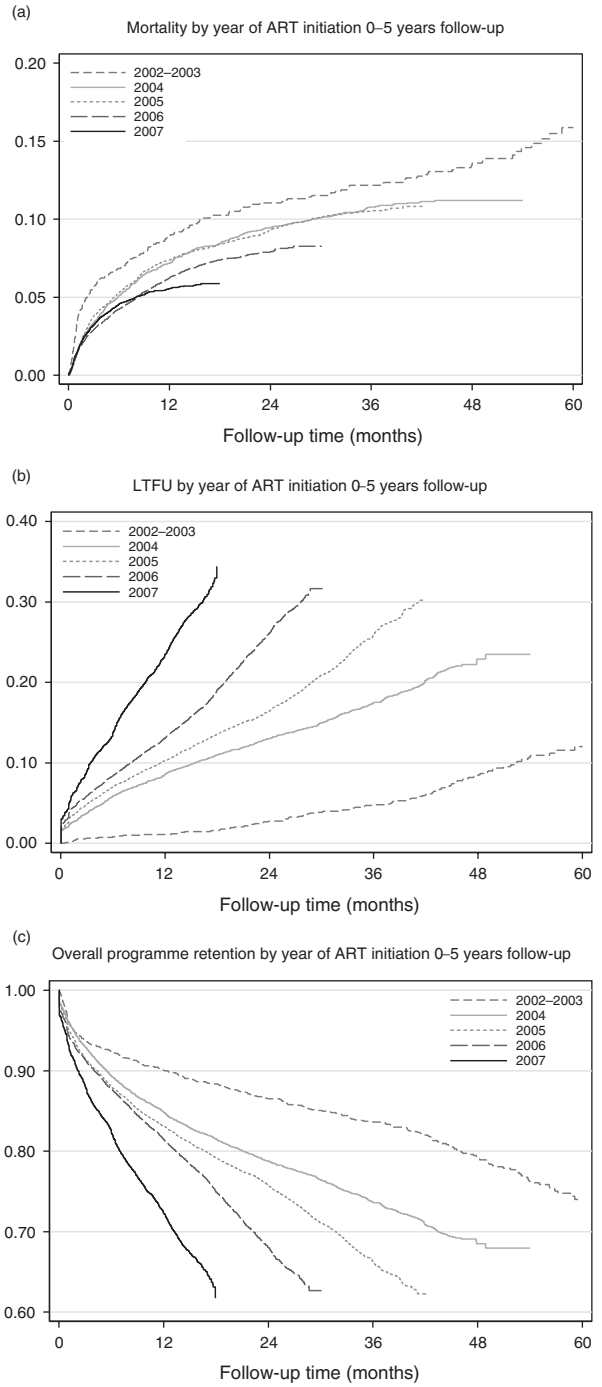

Fig. 1. Kaplan-Meier plots showing by year of ART initiation: (a) 60-month mortality, (b) 60-month loss-to-follow-up and (c) 60-month programme retention.

first 4 months on ART among those enrolled in 2007 was 31% lower than in those enrolled in 2002/2003 (adjusted HR 0.69, 95% CI 0.52–0.91). Similar results were found in the later durations on treatment.

CD4 cell count was strongly associated with early mortality on ART in both crude and adjusted analyses: in the first four months on ART, patients with CD4 cell count below 50 cells/μl had a six-fold higher risk of mortality than those with CD4 cell count at least 200 cells/μl (adjusted HR 5.85, 95% CI 4.47–7.65, Table 4). With longer duration on ART, patients with baseline CD4 cells count below 50 cell/μl continued to be at an elevated risk of death compared with those above 200 cells/μl: the risk was nearly three-fold higher for patients 4–12 months on treatment (adjusted HR 2.83, 95% CI 2.08–3.85) and two-fold higher for patients 12–36 months on ART (adjusted HR 1.84, 95% CI 1.24–2.71). The addition of WHO staging attenuated the association between CD4 cell count and death over all durations on ART, particularly in the group of patients with CD4 cell count 50–199 cells/μl at baseline.

In univariate and multivariate analysis, younger patients were more likely to be LTFU than older (adjusted HR 0.99, 95% CI 0.98–0.99, Table 5). Year of enrolment strongly predicted the risk of LTFU in the early and later time periods on ART: the risk of LTFU increased substantially with each successive year of enrolment and the strength of the association persisted after controlling for baseline age and CD4 cell count. After adjustment for these factors, patients enrolled on ART in 2007 had a 12-fold increase in the risk of being LTFU during the first year on ART compared with those starting treatment in 2002/2003 (adjusted HR 11.89, 95% CI 6.36–22.25). Those with a baseline CD4 cell count 50–199 cells/μl were less likely to be LTFU in the first year on treatment than those with a CD4 cell count ≥200 (adjusted HR 0.83, 95% CI 0.76–0.91). This association did not persist when WHO staging was added to the model (adjusted HR 1.03, 95% CI 0.77–1.38).

Discussion

This analysis demonstrates the increasing role played by LTFU over time in the outcomes of the South African national ART programme. The rapid pace of ART scale-up in South Africa is evident from the 12-fold increase in this analysis in the number of patients starting ART since 2002/2003, with 63% of all patients initiating ART during 2006 and 2007 alone. While recorded mortality has declined during this period, observed LTFU has increased substantially and presents a major threat to evaluating the effectiveness of the national programme.

Patient retention is a vital measure of the effectiveness of ART services [6,7]. Retention in long-term care is complex, especially in low-income and middle-income countries [8–10], but not a new issue: primary healthcare services have long faced the problem of patient attrition in providing care for chronic diseases [6,11]. A systematic review of ART programmes in sub-Saharan Africa found large variation in patient retention across programmes, ranging from 46 to 85% after 2 years on ART [12]. At the

Table 3. Kaplan–Meier estimates of mortality, loss-to-follow-up and overall programme retention by duration of follow-up ($n = 44\,177$ at baseline).

Duration of follow-up	*n* (%)	Mortality % (95% CI)	Loss-to-follow-up % (95% CI)	Overall retention % (95% CI)
6 months	35 627 (80.6)	4.8 (4.6–5.0)	9.3 (9.0–9.6)	86.4 (86.1–86.7)
12 months	26 315 (59.6)	6.6 (6.3–6.8)	14.4 (14.1–14.8)	80.0 (79.6–80.3)
18 months	18 788 (42.5)	7.6 (7.4–7.9)	18.8 (18.4–19.3)	75.0 (74.5–75.4)
24 months	13 115 (29.7)	8.5 (8.2–8.8)	22.4 (21.9–22.9)	71.0 (70.5–71.5)
36 months	5486 (12.4)	9.7 (9.4–10.1)	28.7 (28.0–29.3)	64.4 (63.8–65.0)
48 months	803 (1.8)	10.6 (10.1–11.2)	33.3 (32.4–34.2)	59.6 (58.7–60.5)
60 months	185 (0.4)	12.9 (11.4–14.7)	35.8 (34.3–37.4)	55.9 (54.1–57.6)

start of the South African national programme, based on experience with other chronic diseases, it was suggested that the ART service might retain 60–80% of patients annually [11]. Retention in the earlier years of the programme exceeded this expectation: at 2 years, 71% of all patients were still known to be in care, but the steady increase in attrition during the first 12 months on ART in successive years of enrolment is cause for concern.

Mortality is one reason for patient attrition: in this cohort, observed mortality at 12 months was 6.6%, which is comparable with results from other developing countries [13]. With successive years of enrolment, 12-month mortality decreased. This may be a true decline due to improved coverage of services and patients enrolling with less advanced HIV disease [14]. It is also plausible that as a programme expands, its ability to accurately ascertain patient deaths deteriorates, and high observed LTFU may be associated with poor mortality ascertainment [15]. It is likely that our study, based on routine surveillance, underestimates true mortality in these cohorts. Recent corrected mortality estimates for single South African ART cohorts (based on linkage to the national death register) found that at 3 years on ART, corrected cumulative mortality was 12–15% [16,17] compared with our uncorrected estimate of 10%. There is an urgent need to improve ascertainment of deaths in low-income and middle-income countries [18–20].

Yet even with such underestimation, mortality is not the major reason for patient attrition in large ART programmes in developing countries. The greater threat to the success of the South African ART programme may be the observation of high levels of LTFU, insofar as this outcome reflects patients who have truly left care. The size and pace of ART scale-up may have contributed to observed LTFU. The programme has grown in size dramatically, with our combined cohort increasing enrolment 12-fold over 5 years. Such rapid increases have placed considerable strain on health services that were already overburdened [8,16,21] and may have undermined the programme's ability to monitor and retain patients in care. During 2007 alone, 33% of patients in this study were enrolled onto ART: compared with the 2002/2003 cohort of patients, they had a 12-fold higher risk of appearing LTFU. In addition, with longer duration on ART, observed LTFU accounted for an increasing proportion of overall programme attrition: from 9% at 6 months to 29% at 36 months on ART.

If the rapid expansion of ART services does increase observed LTFU, the situation may worsen as countries continue to expand access to HIV treatment. Based on 2002 WHO treatment guidelines, adult ART coverage in South Africa was an estimated 40% in 2008 [22]. In addition, the South African government recently revised its treatment guidelines to include all infected infants <1 year of age, pregnant women with CD4 cell counts of 350 cells/μl or less and patients co-infected with TB [23]. South Africa and many other countries in sub-Saharan Africa will need to continue to expand services while retaining large numbers of patients in care. This will require strengthening systems for chronic disease care in these countries [6], where most health programmes are oriented towards episodic illnesses and acute care.

Successfully re-orienting health systems towards long-term chronic care will require a better understanding of the phenomenon of LTFU. Often viewed as a single construct, observed LTFU in an ART cohort more likely represents a range of patient outcomes including patients truly LTFU (i.e. lost to care) as well as those classified LTFU through administrative error or inadequate patient monitoring systems [15,24]. In a situation of rapid scale-up of ART in resource-limited health systems, the ability to capture and report patient data may become increasingly inadequate [24]. Indeed, our results suggest that larger cohorts may have become more subject to these challenges in recent years. For example, the apparently sharp increase in observed LTFU among patients enrolled in 2007 is likely to reflect the cumulative burden of increasing patient numbers on both ART services and health informatics systems. This phenomenon may be particularly acute at larger and rapidly expanding ART sites, some of which enrolled up to 50% of their cumulative number of patients in 2007 alone.

Despite the scope of the problem of observed LTFU in ART services in southern Africa, relatively little is known about this phenomenon. These cohorts, which are largely

Table 4. Cox's proportional hazards models of 0–4 months, 4–12 months and 12–36 months mortality by baseline characteristics and year of ART initiation, stratified by cohort. Multivariate models adjusted for all variables shown (Model 1 excludes WHO staging; Model 2 includes WHO staging).

	0–4 months			4–12 months			12–36 months		
		Multivariate models			Multivariate models			Multivariate models	
Variables	Univariate HR (95% CI)	Model 1 ($n=36\,549$) HR (95% CI)	Model 2 ($n=9951$) HR (95% CI)	Univariate HR (95% CI)	Model 1 ($n=31\,038$) HR (95% CI)	Model 2 ($n=8343$) HR (95% CI)	Univariate HR (95% CI)	Model 1 ($n=21\,992$) HR (95% CI)	Model 2 ($n=6055$) HR (95% CI)
Age (years)	1.01 (1.00–1.02)	1.01 (1.00–1.01)	1.01 (1.00–1.02)	1.02 (1.01–1.02)	1.02 (1.01–1.03)	1.03 (1.01–1.04)	1.03 (1.02–1.04)	1.03 (1.02–1.04)	1.05 (1.03–1.07)
Year of enrolment									
2002/2003	1	1	1	1	1	1	1	1	1
2004	0.65 (0.50–0.86)	0.62 (0.46–0.82)	0.82 (0.60–1.13)	1.03 (0.70–1.53)	0.89 (0.59–1.35)	0.98 (0.61–1.57)	1.13 (0.78–1.65)	1.03 (0.68–1.57)	1.01 (0.67–1.59)
2005	0.71 (0.55–0.91)	0.73 (0.56–0.96)	0.70 (0.62–0.96)	0.95 (0.65–1.39)	0.87 (0.58–1.30)	0.85 (0.54–1.33)	0.86 (0.60–1.27)	0.82 (0.54–1.25)	0.73 (0.45–1.20)
2006	0.56 (0.43–0.72)	0.62 (0.47–0.81)	0.62 (0.45–0.85)	0.83 (0.57–1.22)	0.73 (0.49–1.10)	0.64 (0.40–1.02)	0.69 (0.45–1.05)	0.66 (0.42–1.06)	0.84 (0.23–1.22)
2007	0.63 (0.49–0.82)	0.69 (0.52–0.91)	0.56 (0.37–0.86)	0.49 (0.32–0.73)	0.47 (0.30–0.72)	1.10 (0.37–3.22)	0.24 (0.11–0.51)	0.25 (0.11–0.57)	–
CD4 cell count (cells/μl)									
≥200	1	1	1	1	1	1	1	1	1
50–199	1.67 (1.27–2.19)	1.64 (1.25–2.16)	0.93 (0.60–1.44)	1.50 (1.11–2.03)	1.41 (1.04–1.91)	0.78 (0.46–1.32)	1.24 (0.85–1.81)	1.16 (0.79–1.69)	1.07 (0.51–2.22)
<50	5.95 (4.55–7.78)	5.85 (4.47–7.65)	2.80 (1.83–4.28)	3.00 (2.21–4.07)	2.83 (2.08–3.85)	1.53 (0.90–2.59)	1.94 (1.31–2.87)	1.84 (1.24–2.71)	1.39 (0.66–2.95)
WHO stage									
I and II	1	–	1	1	–	1	1	–	1
III	3.27 (2.03–5.28)	–	2.35 (1.41–3.91)	2.01 (1.21–3.34)	–	1.49 (0.87–2.53)	1.48 (0.83–2.66)	–	1.32 (0.72–2.54)
IV	10.21 (6.41–16.26)	–	5.82 (3.51–9.62)	4.12 (2.50–6.79)	–	2.78 (1.62–4.74)	2.54 (1.43–4.52)	–	1.98 (1.04–3.75)
HIV RNA level, $\log_{10}$ copies/ml									
≤5 Log	1	–	–	1	–	–	1	–	–
>5 Log	1.90 (1.63–2.22)	–	–	1.32 (1.09–1.59)	–	–	1.42 (1.12–1.82)	–	–

Table 5. Cox's proportional hazards models of LTFU at 0–12 months and 12–36 months by baseline characteristics and year of ART initiation, stratified by cohort. Multivariate models adjusted for all variables shown (Model 1 excludes WHO staging; Model 2 includes WHO staging).

	0–12 months			12–36 months		
		Multivariate models			Multivariate models	
Variables	Univariate HR (95% CI)	Model 1 ($n=36\,549$) HR (95% CI)	Model 2 ($n=9951$) HR (95% CI)	Univariate HR (95% CI)	Model 1 ($n=21\,992$) HR (95% CI)	Model 2 ($n=6055$) HR (95% CI)
Age (years)	0.99* (0.99–0.99)	0.99** (0.99–0.99)	0.98 (0.97–0.99)	0.99 (0.98–0.99)	0.99 (0.98–0.99)	0.97 (0.96–0.99)
Year of enrolment						
2002/2003	1	1	1	1	1	1
2004	6.69 (3.77–11.89)	5.74 (3.06–10.79)	2.63 (1.29–5.39)	2.76 (1.96–3.89)	3.37 (2.20–5.15)	3.54 (2.17–5.77)
2005	7.68 (4.34–13.59)	6.29 (3.36–11.76)	4.99 (2.54–9.80)	4.13 (2.92–5.84)	4.98 (3.25–7.65)	6.57 (3.94–10.93)
2006	9.40 (5.32–16.61)	7.67 (4.10–14.34)	9.27 (4.76–18.05)	7.27 (5.11–10.35)	8.01 (5.17–12.40)	10.62 (5.73–19.68)
2007	15.34 (8.68–27.13)	11.89 (6.36–22.25)	10.89 (5.47–22.10)	12.77 (8.78–18.59)	12.58 (7.91–20.00)	–
CD4 cell count (cells/μl)						
≥200	1	1	1	1	1	1
50–199	0.77 (0.71–0.85)	0.83 (0.76–0.91)	1.03 (0.77–1.38)	0.92 (0.80–1.07)	0.98 (0.85–1.14)	0.55 (0.39–0.78)
<50	0.97 (0.88–1.07)	1.05 (0.95–1.15)	1.30 (0.95–1.79)	0.85 (0.72–1.00)	0.91 (0.77–1.08)	0.56 (0.38–0.83)
WHO stage						
I and II	1	–	1	1	–	1
III	0.98 (0.79–1.21)	–	1.16 (0.92–1.46)	0.86 (0.65–1.13)	–	1.07 (0.78–1.45)
IV	1.12 (0.90–1.39)	–	1.35 (1.04–1.74)	0.67 (0.49–0.91)	–	0.95 (0.68–1.35)
HIV RNA level, $\log_{10}$ copies/ml						
≤5 Log	1	–	–	1	–	–
>5 Log	0.98 (0.89–1.08)	–	–	0.92 (0.81–1.03)	–	–

*0.989 (0.986–0.993).
**0.989 (0.985–0.992).

funded by the national Department of Health, report active tracing (i.e. dedicated resources to undertake one or more of the following: telephone call, home follow-up, physician's report and/or data linkage) [3]. However, largely due to resource constraints, funding for patient follow-up, particularly at this scale, is limited. There is a small literature on factors associated with patient retention highlighting the possible role of patient preparation [25], treatment supporters [26], patient costs [10,27], improved databases [24], community support [28] and simplified services [6]. However, research is needed to better understand observed LTFU and the relative contributions of true LTFU (patients dropping out of ART services) versus administrative LTFU (patients who are retained in care but appear LTFU due to problems with data capturing and reporting). In contrast to these individuals, patients who are truly LTFU are likely to be nonadherent to treatment and at higher risk of death [16,29]. In addition, they face increased risk of drug resistance to ART, undermining the long-term effectiveness of treatment programmes [12,16]. Additional research is needed into the programme-level determinants of LTFU, to better characterise patients classified LTFU and provide insights into patients' movements in and out of care.

This is the first report on outcomes from multiple cohorts in the world's largest antiretroviral therapy programme, and to our knowledge, the largest analysis of individuals starting ART in sub-Saharan Africa. It is strengthened by up to 5 years of patient follow-up on more than 40 000 patients. The results are likely generalizable to the patient population accessing public sector ART in most of South Africa [3] where 80% of the population rely on the public sector for services [30]. However, this analysis has several important limitations. As is the case with other large-scale ART programmes based on routine monitoring and evaluation, it is constrained by issues of outcome ascertainment and missing data [24]. Outcome ascertainment should improve as more cohorts in South Africa link to the death register, presumably increasing observed mortality and decreasing observed LTFU. Data completeness is likely to present ongoing challenges, particularly as programmes continue to expand. WHO staging were the least complete data point in this analysis, yet the inclusion of staging in multivariate analysis impacted on the association between baseline CD4 cell count and outcomes, highlighting the importance of complete baseline data. Finally, this paper reports on averages across cohorts, which may differ in data quality, completeness and outcome ascertainment. Despite these constraints, this analysis utilizes routinely collected data to provide valuable insight into the effectiveness of a huge national programme, and has important implications for South Africa and for other programmes in similar contexts.

In summary, this analysis demonstrates that the South African national ART programme has undergone rapid scale-up over 5 years. While recorded mortality has declined, programme retention has deteriorated as decreasing patient mortality has been greatly offset by high and increasing levels of LTFU. This increased LTFU may represent true loss to care, but also may be due to increasing difficulty in monitoring patients enrolling into care as well as patient movements in and out of care. These possibilities require further investigation. Innovative, effective strategies are needed to follow and retain patients in large HIV treatment programmes while rapidly expanding access to ART services.

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