Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa

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Objectives: We report on outcomes after 7 years of a community-based antiretroviral therapy (ART) programme in Khayelitsha, South Africa, with death registry linkages to correct for mortality under-ascertainment.

Design: This is an observational cohort study.

Methods: Since inception, patient-level clinical data have been prospectively captured on-site into an electronic patient information system. Patients with available civil identification numbers who were lost to follow-up were matched with the national death registry to ascertain their vital status. Corrected mortality estimates weighted these patients to represent all patients lost to follow-up. CD4 cell count outcomes were reported conditioned on continuous virological suppression.

Results: Seven thousand, three hundred and twenty-three treatment-naive adults (68% women) started ART between 2001 and 2007, with annual enrolment increasing from 80 in 2001 to 2087 in 2006. Of 9.8% of patients lost to follow-up for at least 6 months, 32.8% had died. Corrected mortality was 20.9% at 5 years (95% confidence interval 17.9–24.3). Mortality fell over time as patients accessed care earlier (median CD4 cell count at enrolment increased from 43 cells/μl in 2001 to 131 cells/μl in 2006). Patients who remained virologically suppressed continued to gain CD4 cells at 5 years (median 22 cells/μl per 6 months). By 5 years, 14.0% of patients had failed virologically and 12.2% had been switched to second-line therapy.

Conclusion: At a time of considerable debate about future global funding of ART programmes in resource-poor settings, this study has demonstrated substantial and durable clinical benefits for those able to access ART throughout this period, in spite of increasing loss to follow-up.

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Introduction

Less than 10 years ago, opinions were divided as to the feasibility of providing antiretroviral therapy (ART) in those countries, mostly in Africa, in which the majority of people living with HIV reside [1,2]. Since then, a number of African ART programmes have demonstrated excellent adherence and clinical outcomes for the first wave of patients accessing care [3–8].

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The focus of attention is now shifting from feasibility to sustainability. Little is known about either the longer term outcomes on ART in these settings or whether the early outcomes have been sustained for patients accessing care more recently. In particular, the true outcomes of patients who are lost to follow-up are hardly known outside of study settings [7,9].

One of the first programmes that demonstrated the feasibility of ART in Southern Africa was the Khayelitsha ART programme [3], established in 2001 by Médecins Sans Frontières and the provincial government of the Western Cape, South Africa. Early outcomes from the Khayelitsha programme helped to establish the importance of a patient-centred adherence model and strong community activism for ART care [10]. This study describes outcomes for adults in Khayelitsha up to 5 years on ART and temporal trends in these outcomes over 7 years, utilizing linkages with the South African vital registration system to correct mortality estimates for increasing loss to follow-up (LTF) in recent years.

Setting

The Khayelitsha HIV treatment programme was established in 2000 at three public sector primary care clinics in Khayelitsha township, home to an estimated 500 000 people. Antenatal HIV prevalence was 22.0% in 2001 and 32.7% in 2007 [11]. ART was first provided through a pilot demonstration project in May 2001, with modest capacity to provide therapy for 180 adults [12]. By the end of 2007, the service had cumulatively enrolled over 7000 treatment-naive adults onto ART and was operating as a routine government service.

Adult patients are eligible for ART if their CD4 cell count drops below 200 cells/μl or if they have a WHO stage IV condition other than extrapulmonary tuberculosis. The initial regimen was zidovudine (ZDV) and lamivudine (3TC) together with nevirapine (NVP) or efavirenz (EFV). Stavudine (d4T) replaced ZDV in the standard first-line regimen in late 2003 in order to align with the South African national guidelines, which were implemented in April 2004 [13]. Viral load (NucliSens EasyQ HIV-1 assay; bioMérieux, Boxtel, The Netherlands) and CD4 cell count (single-platform panleucogating method) [14] testing are provided 6-monthly after starting ART. Serum alanine aminotransferase and haemoglobin are monitored for patients on NVP and ZDV, respectively. Guidelines make provision for a second-line regimen (ZDV, didanosine and lopinavir/ritonavir) to be started after virological failure is confirmed (two consecutive viral load results $\geq$5000 copies/ml, in spite of enhanced adherence promotion after the first elevated result).

The major sources of referral to the service are from acute care and tuberculosis services in the subdistrict. Nurse-based care has been central to this treatment programme since inception with more than two-thirds of consultations with nurses, and this model of care has continued to evolve over time. The frequency and intensity of clinical contact has decreased, with stable patients seen by a nurse 2 or 3-monthly, and many of the consultations for long-term stable patients being integrated into group sessions ('clubs'). The adherence model remains patient-centred but no longer includes routine home visits or a signed patient contract. Pharmacist assistants now dispense most drugs, and doctors see patients predominantly on the basis of internal referral of patients by nurses.

Prevention of mother-to-child transmission (PMTCT) services have been available since 1999, initially based on short-course ZDV [15], and since late 2003, on both short-course ZDV and peripartum NVP in women not eligible for triple therapy [16]. Data on the type of PMTCT received were not available for this analysis.

Methods

Data management and processing

Clinicians have used structured clinical records throughout the period of analysis, which are captured on-site into an electronic patient information system by dedicated data capturers. All clinical care, record keeping and data capture are part of routine patient management as per provincial guidelines. Rule-based consistency checks identify specific patients and data elements for review by quality assurance staff.

This analysis includes all data on treatment-naive patients (including those exposed only to PMTCT interventions) of age 14 years and older, until the end of 2007. Mortality and LTF estimates include patients enrolled until the middle of 2007 in order to give all patients the opportunity of meeting the LTF definition of 6 months without a clinic visit. When adjusting analyses for the year of enrolment, the first 2 years were combined into a single period due to the small numbers enrolled in these years and similarity in patient profile.

Civil identification numbers, where available, were cross-checked in the national death registry to confirm or ascertain dates of death for those with registered deaths. It was not possible to differentiate deaths due to HIV from deaths due to other causes. All data were anonymized prior to being made available for analysis.

Follow-up laboratory results were considered as representing the nearest 6-monthly follow-up duration. Baseline CD4 cell counts included measures from

12 months prior to 1-week posttreatment initiation. If more than one measure was available, the measure closest to baseline or 6-monthly duration was used. When comparing viral loads on first and second-line regimens, first-line viral loads were restricted to tests done prior to the switching. Second-line viral loads were restricted to measures that followed the initiation of second-line by at least 3 months in order to exclude repeated baseline viral loads at the initiation of second-line. Laboratory outcomes are presented only for those patients on treatment in whom test results were available, and no assumption is made on laboratory outcomes in those who missed a scheduled test or who were lost to care at the time.

Analysis

Kaplan–Meier estimates of time to death and LTF (date last seen) are described. A weighted Kaplan–Meier approach was used to correct the mortality estimate for those who were LTF but had died, by weighting those patients who were LTF but for whom a definitive outcome could be established from the death registry, to represent all patients lost to follow-up [17]. Weights were calculated separately by year and duration of follow-up. Bootstrap confidence intervals (CIs) for the weighted Kaplan–Meier failure estimates were calculated by sampling from the dataset with replacement 1000 times. Patients who were known to have transferred to other services were right censored at the date of transfer. Cox proportional hazard models based on the same weighted data were used to explore associations with early (<3 months) and late mortality.

Virological responses were described as the proportion below 400 copies/ml at each year of follow-up for all patients, and separately for patients on first and second-line regimens. Virological responses on first and second-line therapy were compared across all durations in a logistic regression model clustered on individuals with robust standard errors. CD4 cell responses were described as median absolute value, change from baseline count and change from previous count at each duration of follow-up. This was repeated on a subset of patients who had been continuously virologically suppressed until the CD4 cell count measure. Proportions were compared using the chi-squared test and medians using the rank sum test.

Time to confirmed virological failure and time to the initiation of second-line therapy were described as standard Kaplan–Meier estimates, and associations with virological failure were explored with a standard Cox model. A population-averaged linear regression model with an exchangeable correlation matrix was used to explore associations with CD4 cell count responses in each 6-month interval, limited to patients with continuous virological suppression.

All analyses were conducted using Stata statistical software, version 10.0 (Stata-Corp Inc., College Station, Texas, USA). The analysis of routine cohort data and the linkage to the national death registry were both approved by the University of Cape Town Research Ethics Committee.

Results

Annual enrolment increased from 80 treatment-naive adult patients in 2001 to 2087 in 2006 (Table 1), with a total of 7323 enrolled during the period under analysis. Women constituted 68.2% of the cohort and were younger at enrolment than men (median 31 vs. 36 years, $P < 0.001$). Overall, 3.7% of women initiated ART while pregnant and 11.1% had previously received PMTCT interventions. Median baseline CD4 cell count increased from 43 [interquartile range (IQR) 13–95] cells/μl in 2001/2002 to 131 (IQR 64–191) cells/μl in 2007. The proportion with clinically advanced disease (AIDS as defined by WHO clinical stage IV) [18,19] decreased over the same period from 54.5 to 28.9%. The proportion initiating ART while already on treatment for tuberculosis increased from 22.7 to 42.4%.

Civil identification numbers were available for 57.0% of all patients and 70.6% of patients enrolled in 2007 (Webtable 1). Cross-sectionally, 9.8% of patients enrolled by the middle of 2007 (628/6402) had been LTF. Just under half of those LTF had a civil identification number (46.7%), of whom 32.8% had a registered death before the end of 2007. Patients lost in their first year of treatment (59.2%) were more likely to have died compared with those lost thereafter (42.4 vs. 18.1%, $P < 0.001$).

In patients whose deaths were reported to the services and for whom a civil identification number was available, 90.5% (172/190) were matched in the death registry, whereas 99.9% (2941/2944) of patients known to be alive and with valid civil identification numbers were not found in the registry, reflecting the sensitivity and specificity of the data linkage.

The cumulative estimate of mortality based on clinic-held data was 15.5% (95% CI 13.1–18.3) at 5 years (Fig. 1a), whereas the equivalent estimate of LTF was 23.4% (95% CI 20.5–26.6). Combining LTF and mortality, 35.3% (95% CI 32.1–38.6) of patients were lost to care at 5 years. LTF has occurred earlier with each successive year of enrolment (Fig. 1b). The weighted estimates of mortality, including patients LTF who could be matched in the death registry, were 9.9% (95% CI 8.9–10.9), 12.6% (95% CI 11.5–13.8) and 20.9% (95% CI 17.9–24.3) at 1, 2 and 5 years, respectively (Fig. 1c). Incorporating the linkage data, overall mortality has decreased over time (Fig. 1d).

Low baseline CD4 cell count, an AIDS diagnosis and a low body weight were all strongly associated with

Table 1. Baseline characteristics of adult patients starting antiretroviral therapy in Khayelitsha: 2001–2007.

Year of starting ART	2001/2002	2003	2004	2005	2006	2007	Combined
Patients enrolled							
n	286	388	1061	1641	2087	1860	7323
Sex, *n* (%)							
Male	85 (29.7)	121 (31.2)	317 (29.9)	492 (30.0)	734 (35.2)	613 (33.0)	2362 (32.3)
Age (years)							
Women, median (IQR)	31 (26–36)	30 (27–34)	31 (27–37)	31 (27–36)	31 (27–38)	31 (27–37)	31 (27–37)
Men, median (IQR)	35 (30–39)	36 (30–41)	36 (31–41)	36 (31–42)	36 (31–42)	37 (32–42)	36 (31–42)
Baseline CD4 cell count (cells/μl)							
Tested (*n*, %)	284 (99.3)	383 (98.7)	1051 (99.1)	1565 (95.4)	1894 (90.8)	1428 (76.8)	6605 (90.2)
Median (IQR)	42.5 (13–95)	72 (22–126)	85 (37–141)	100 (44–157)	109 (52–169)	131 (64–191)	101 (45–164)
Baseline viral load (copies/ml)							
Tested (*n*, %)	271 (94.8)	263 (67.8)	927 (87.4)	1481 (90.2)	519 (24.9)	26 (1.4)	3487 (47.6)
Log_{10} median (IQR)	5.1 (4.7–5.6)	5.2 (4.6–5.6)	5.2 (4.7–5.7)	5.0 (4.5–5.5)	5.0 (4.5–5.6)	4.6 (4.0–5.4)	5.1 (4.6–5.6)
WHO stage, *n* (%)							
I/II	2 (0.7)	6 (1.5)	102 (9.6)	240 (14.6)	374 (17.9)	428 (23.0)	1152 (15.7)
III	128 (44.8)	183 (47.2)	514 (48.4)	791 (48.2)	1062 (50.9)	893 (48.0)	3571 (48.8)
IV	156 (54.5)	199 (51.3)	445 (41.9)	610 (37.2)	651 (31.2)	538 (28.9)	2599 (35.5)
Weight (kg)							
Tested (*n*, %)	285 (99.7)	379 (97.7)	1026 (96.7)	1563 (95.2)	2037 (97.6)	1532 (82.4)	6822 (93.2)
Median (IQR)	56.8 (50.0–65.0)	59 (50.0–68.0)	59 (52.0–66.5)	58 (51.5–66.5)	59.3 (52.0–67.2)	60 (52.2–68.0)	59 (51.6–67.0)
Tuberculosis							
n (%)	65 (22.7)	105 (27.1)	316 (29.8)	618 (37.7)	867 (41.5)	789 (42.4)	2760 (37.7)
Pregnant							
n (% of women)	1 (0.5)	3 (1.1)	14 (1.9)	53 (4.6)	38 (2.8)	75 (6.0)	184 (3.7)
PMTCT exposed							
n (% of women)	26 (12.9)	47 (17.6)	108 (14.5)	163 (14.2)	119 (8.8)	88 (7.1)	551 (11.1)
Baseline regimen, *n* (%)							
ZDV/3TC/EFV	170 (59.4)	247 (63.7)	6 (0.6)	32 (2.0)	93 (4.5)	94 (5.1)	642 (8.8)
ZDV/3TC/NVP	108 (37.8)	17 (4.4)	16 (1.5)	63 (3.8)	150 (7.2)	258 (13.9)	612 (8.4)
D4T/3TC/EFV	2 (0.7)	106 (27.3)	279 (26.3)	859 (52.3)	1058 (50.7)	887 (47.7)	3191 (43.6)
D4T/3TC/NVP	2 (0.7)	17 (4.4)	759 (71.5)	687 (41.9)	774 (37.1)	579 (31.1)	2818 (38.5)
Other	4 (1.4)	1 (0.3)	1 (0.1)	0 (0.0)	12 (0.6)	42 (2.3)	60 (0.8)

3TC, lamivudine; ART, antiretroviral therapy; D4T, stavudine; EFV, efavirenz; IQR, interquartile range; NVP, nevirapine; ZDV, zidovudine.

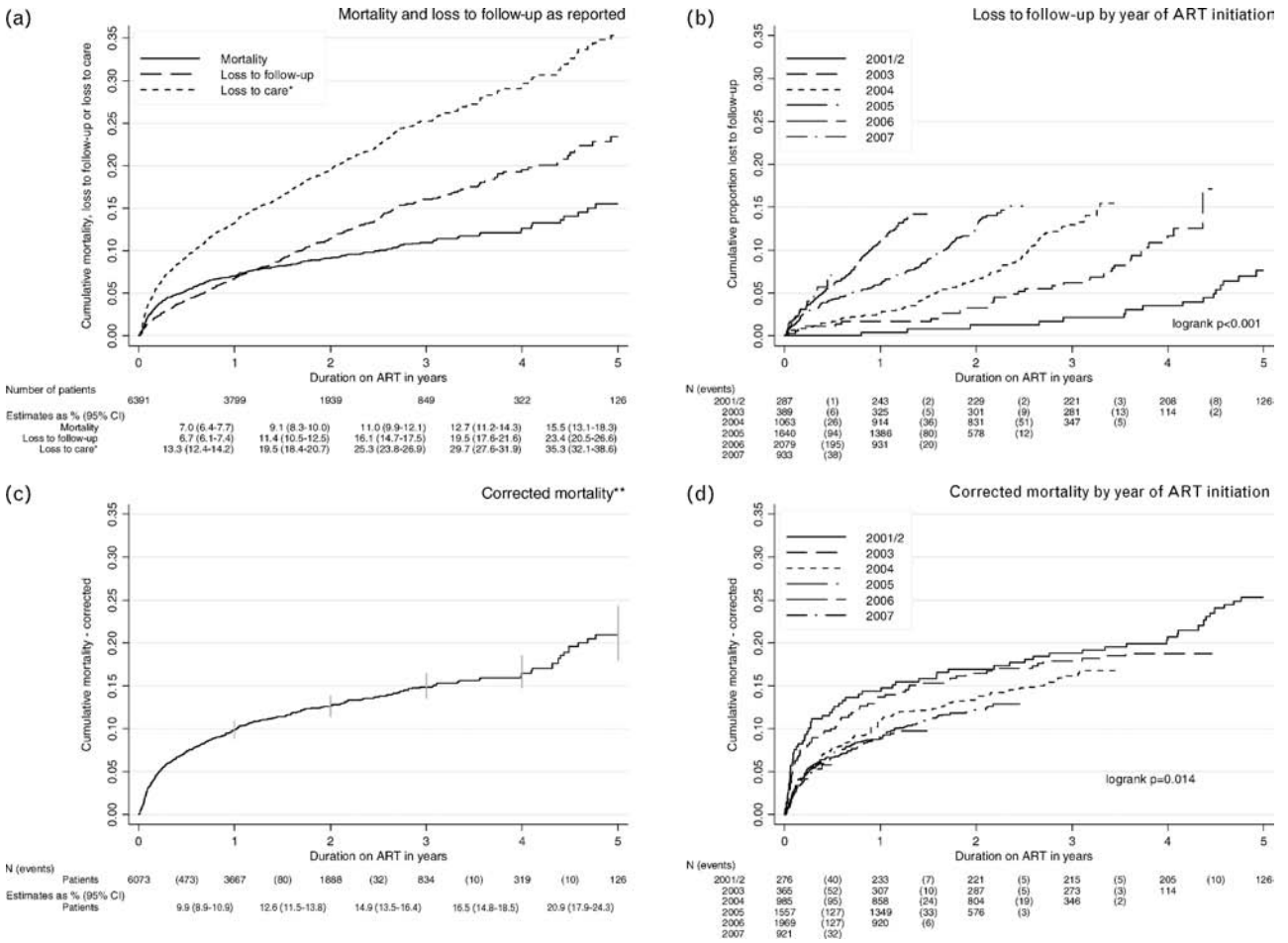

Fig. 1. Cumulative estimates of mortality, loss to follow-up and loss to care. Kaplan–Meier estimates of reported mortality and loss to follow-up (a), loss to follow-up by year of initiation (b), corrected mortality (c) and corrected mortality by year of initiation (d). ART, antiretroviral therapy; CI, confidence interval. *Loss to care includes both those who have died and those lost to follow-up. **Vital status was ascertained for patients lost to follow-up from the national death registry if a civil identification number was available. These patients were weighted in this analysis to represent all patients lost to follow-up. Vertical bars represent 95% CIs.

mortality in the first 3 months on ART (Table 2) and remained associated, although attenuated, beyond 3 months. Older age (>50 years) was associated with higher mortality after 3 months on ART. Year of ART initiation was not associated with mortality after adjustment for baseline characteristics.

For all patients combined, 87.6, 88.1 and 83.8% of those who remained in care and received viral load tests were virologically suppressed (<400 copies/ml) at 1, 3 and 5 years, respectively (Table 3). Patients on second-line ART were less likely to be virologically suppressed compared with patients remaining on first line at equivalent durations on ART [odds ratio (OR) 0.51, 95% CI 0.26–1.01], although 22 out of 29 (75.9%) patients on second-line ART at 5 years were virologically suppressed.

Patients who remained virologically suppressed throughout follow-up had gained a median of 474 (IQR 341–660) CD4 cells/μl by 5 years and continued to gain a median of 22 cells/μl per 6-month period between 4 and 5 years on ART (Table 3). Additional factors independently associated with CD4 cell count gain (Table 4) were female sex, younger age and measures of disease advancement at ART initiation (AIDS, tuberculosis and low CD4 cell count). At 5 years on ART, 3.7, 11.9 and 25.7% of virologically suppressed patients had CD4 count values less than 200, 200–349 and 350–499 cells/μl, respectively.

By 5 years, 14.0% (95% CI 11.9–16.4) of patients had met the guideline definition of confirmed virological failure (Fig. 2) and 12.2% (95% CI 10.1–14.8) had started second-line therapy. Seventy-four percent of those starting second-line therapy formally met the guideline definition and started second line a median 5.3 (IQR 2.2–11.2) months after the date of the second raised viral load. The remaining patients were started on second-line therapy with one of the raised values being between 400 and 5000 copies/ml or without a confirmatory viral load test.

Table 2. Characteristics at the start of antiretroviral treatment associated with mortality in multivariate weighted Cox proportional hazard models.

	First 3 months on ART[a]			Beyond 3 months on ART[b]		
	AHR	95% CI	*P*	AHR	95% CI	*P*
Age ≥50 years	1.2	0.7–2.3	0.523	2.3	1.4–3.6	<0.001
Male sex	1.2	0.9–1.6	0.160	1.3	1.0–1.7	0.071
CD4 cell count category (cells/μl)			<0.001			0.003
0–50	3.9	2.3–6.6		1.8	1.2–2.6	
50–149	1.9	1.2–3.3		1.2	0.8–1.7	
150–249 (ref.)	1.0	–		1.0	–	
AIDS diagnosis when starting ART	1.8	1.3–2.4	<0.001	1.4	1.0–1.9	0.038
Baseline weight (per 10 kg)	0.6	0.5–0.6	<0.001	0.8	0.7–0.9	<0.001
Was on TB treatment when starting ART	1.1	0.8–1.4	0.509	0.7	0.5–1.0	0.071
Year of starting ART			0.275			0.941
2001/2002	1.3	0.7–2.5		1.2	0.3–5.1	
2003	1.2	0.6–2.1		1.2	0.3–5.5	
2004	0.7	0.4–1.3		1.4	0.3–6.2	
2005	1.0	0.6–1.7		1.2	0.3–5.0	
2006	1.0	0.6–1.7		1.1	0.3–4.7	
2007 (ref.)	1.0	–		1.0	–	

AHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; TB, tuberculosis.
[a]5346 observations, weighted $n = 5631$.
[b]4833 observations, weighted $n = 4931$.

ART interruptions, PMTCT exposure, low initial CD4 cell count and the use of NVP (especially concomitantly with treatment for tuberculosis) were all independently associated with virological failure (Table 5).

Discussion

Our analysis demonstrates that ART benefits, in a poorly resourced primary care setting, are durable, with almost

Table 3. Viral load and CD4 cell count responses for up to 5 years on antiretroviral therapy.

	1 year	2 years	3 years	4 years	5 years
Viral load					
Combined					
Total in care	4512	2561	1235	458	191
Tested (%)	3932 (87.1)	2198 (85.8)	983 (79.6)	351 (76.6)	148 (77.5)
Suppressed (%) [<400 copies/ml]	3446 (87.6)	1905 (86.7)	866 (88.1)	311 (88.6)	124 (83.8)
First line					
Total in care (%)	4505 (99.8)	2506 (97.9)	1147 (92.9)	405 (88.4)	155 (81.2)
Tested (%)	3890 (86.3)	2127 (84.9)	914 (79.7)	310 (76.5)	119 (76.8)
Suppressed (%) [<400 copies/ml]	3407 (87.6)	1851 (87.0)	812 (88.8)	282 (91.0)	102 (85.7)
Second line					
Total in care (%)	7 (0.2)	55 (2.1)	88 (7.1)	53 (11.6)	36 (18.8)
Tested (%)	5 (71.4)	47 (85.5)	63 (71.6)	41 (77.4)	29 (80.6)
Suppressed (%) [<400 copies/ml]	4 (80.0)	31 (66.0)	50 (79.4)	29 (70.7)	22 (75.9)
CD4 cell count					
All patients					
Total in care	4512	2561	1235	458	191
Tests available	3823	2108	931	341	127
CD4 cell count, median, cells/μl (IQR)	297 (209–397)	383 (276–515)	425.5 (309.5–581)	486 (346.5–669)	512 (353–689)
Change from baseline, median (IQR)	192 (116–282)	282 (180–406)	341 (224–488)	413 (263–580)	442 (266–615)
Change over 6 months, median (IQR)	51 (−7 to 111)	43 (−18 to 111)	24.5 (−55 to 99.5)	20.5 (−54.5 to 124.5)	6 (−85 to 116)
Patients with continuous viral load suppression documented					
Tests available	3380	1847	820	307	109
CD4 cell count, median, cells/μl (IQR)	304 (218–404)	398 (299–531)	459.5 (341.5–601)	511 (391–714)	542 (393–725)
Change from baseline, median (IQR)	198 (124–288)	300 (203–420)	371 (251–509)	441 (317–629)	474 (340.5–659.5)
Change over 6 months, median (IQR)	55 (2–116)	49 (−11 to 117)	34 (−44 to 105)	32.5 (−51 to 141)	22 (−78 to 147)

IQR, interquartile range.

Table 4. Multivariate associations with 6-monthly CD4 cell count changes.

	CD4 cell count changes[a] over 6 months		
	Coefficient[b]	95% CI	*P*
Male sex	−14.3	−17.1 to −11.5	<0.001
AIDS diagnosis at the start of ART	3.0	0.4–5.7	0.026
Had TB at the start of ART	4.7	1.8–7.6	0.002
Age at the start of ART (years)			0.107
16–24 (ref)	0.0	–	
25–49	−4.5	−9.1 to 0.1	
≥50	−7.4	−15.4 to 0.6	
CD4 cell count at the start of ART (cells/μl)			<0.001
0–50	13.2	9.7–16.7	
50–149	2.2	−1.1 to 5.5	
150–249 (ref.)	0.0	–	
Duration of ART (months)			<0.001
6	122.7	117.6–127.9	
12–30	25.2	20.5–29.9	
≥30 (ref.)	0.0		
Constant	33.7	27.6–39.7	

ART, antiretroviral therapy; CI, confidence interval; TB, tuberculosis.
[a]CD4 cell count changes are change for each 6-monthly interval in patients who continuously had viral loads below 400 copies/ml up until the time of the second CD4 cell count measurement. Population-averaged linear regression model with an exchangeable correlation matrix, clustered on individual patient. Thirteen thousand and forty-five observations are reported in 4314 patients.
[b]Adjusted for other variables.

80% of patients remaining alive at 5 years, of whom more than 80% of those tested were virologically suppressed. Improvements in CD4 cell count and clinical stage at ART initiation were translated in absolute terms into improved survival since 2004. After adjustment for these measures, we found that the rapid scale-up in patient numbers has not resulted in increased mortality. Although the link between improved access to care and reduced early mortality has been previously reported in the broader provincial programme of which the Khayelitsha cohort is a part [7], the current analysis was able to correct for possible underascertainment of mortality.

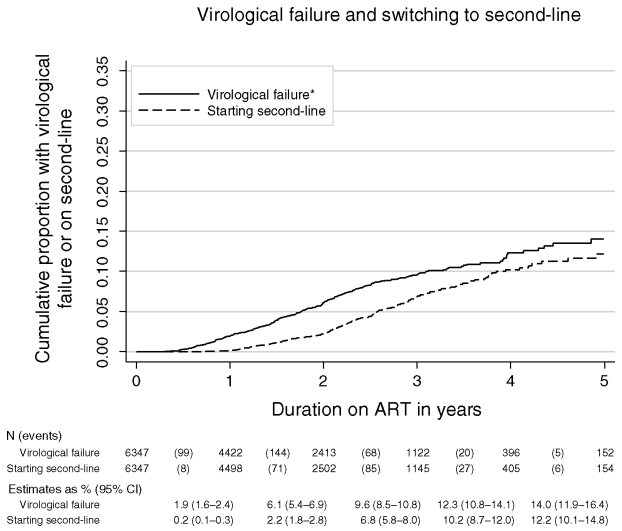

Fig. 2. Time to virological failure and starting second-line therapy. *Virological failure defined as two consecutive viral loads above 5000 copies/ml, at the time of the second elevated value. ART, antiretroviral therapy; CI, confidence interval.

The relatively high proportion of patients who have remained virologically suppressed for up to 5 years on treatment is reassuring. Nevertheless, almost one in five patients reaching 5 years are on a second-line regimen in spite of the delays in switching to second line, suggesting that a substantial number of patients are going to need to access second-line therapy as programmes mature. Predictors of both virological failure and CD4 cell count gain conditioned on continuous virological suppression are rarely reported from scale-up settings. The association between virological failure and PMTCT exposure, in spite of the likely misclassification of some non-NVP exposures, adds to concerns that NVP-based PMTCT may compromise future ART effectiveness [20,21]. The 1.6-fold increased risk of virological failure following each treatment interruption is also of concern, especially given the high proportion of patients who develop serious toxicity on the current first-line regimens in use, which often necessitates treatment interruption [22], and that the majority of interruptions in patients lost to follow-up will not be staggered to cover the longer half-life of non-nucleoside reverse transcriptase inhibitors (NNRTIs) [23,24].

Patients in this cohort who remained virologically suppressed continued to restore CD4 cells throughout follow-up, with the rate of increase slowing as CD4 cell counts reached the normal range. This finding is similar to the equivalent subgroups of patients in recent analyses of European and North American cohorts [25,26] but differs from a collaborative analysis from resource-limited

Table 5. Multivariate associations with confirmed virological failure.

	Virological failure[a]		
	AHR	95% CI	*P*
Male sex	1.0	0.8–1.3	0.977
Exposed to PMTCT prior to ART	1.5	1.1–2.0	0.024
Interruptions to ART (per interruption ≥7 days)	1.6	1.1–2.2	0.012
Age at the start of ART (years)			<0.001
16–24	2.0	1.5–2.7	
25–49 (ref.)	1.0	–	
≥50	0.9	0.5–1.7	
CD4 cell count at the start of ART (cells/μl)			0.009
0–50	1.7	1.2–2.3	
50–149	1.4	1.0–1.9	
150–249 (ref.)	1.0	–	
NNRTI used and TB status at the start of ART			0.002
EFV, no TB (ref.)	1.0	–	
EFV, TB	1.3	0.9–1.9	
NVP, no TB	1.5	1.1–2.1	
NVP, TB	2.5	1.6–4.1	
Year of ART initiation			<0.001
2001/2002	2.1	1.4–3.0	
2003	1.3	0.8–2.0	
2004	0.9	0.7–1.3	
2005 (ref)	1.0	–	
2006	1.1	0.8–1.6	
2007	0.7	0.2–1.8	

AHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PMTCT, prevention of mother-to-child transmission of HIV; TB, tuberculosis.
[a]Virological failure defined as two consecutive viral loads of at least 5000 copies/ml; $n = 5743$, Cox proportional hazards model.

settings, which was not conditioned on viral load suppression [27]. The negative associations between CD4 cell count response and older age and male sex have also previously been described [27]. In total, after 5 years, 41.3% of virologically suppressed patients had a CD4 cell count below 500 cells/μl compared with 35.8% in a comparable study in Switzerland [28]. This difference is most likely the result of the lower baseline CD4 cell counts of patients in Khayelitsha and highlights how advanced disease at enrolment results in more time spent in CD4 cell count strata that carry substantial morbidity and mortality [29].

It is well established that immunological measures are poorly predictive of virological failure [30–33]. In spite of the controversies around the utility of viral load monitoring in this setting [34,35], there is extensive pressure for the more widespread availability of viral load monitoring [36]. The current study is one of the very few in southern Africa to report on the systematic use of viral load testing to identify treatment failure. Applied in a context of rapid scale-up, the South African guidelines still result in an average delay of many months between the first evidence of failure and subsequent switching. This is the result of the time taken to confirm the failure, the pressures on service providers due to increasing patient numbers and a reluctance on the part of clinicians to commit patients to second-line therapy before adherence issues have been exhaustively addressed.

It is unknown whether the delays in switching therapy in viraemic patients as described in our study compromise the effectiveness of subsequent regimens or whether there would be additional consequences of leaving patients on their first-line regimen until they fail immunologically. Two recent African studies [37,38] reported genotypic resistance data at the time of failure of first-line ART. As expected, both studies reported widespread resistance to 3TC and NNRTIs. The Malawian study, in which viral load monitoring is not available, reported a high prevalence of thymidine analogue mutations and the K65R mutation, but the South African study, in which viral load monitoring is available, reported a much lower prevalence of these mutations, suggesting that virological monitoring will better preserve future treatment options. With increasing numbers of patients on second-line regimens, however, some of whom are already failing second line, pressure for a third-line regimen in resource-limited settings is emerging and there is more concern from clinicians about switching too late than too early.

Many of those who have failed virologically and switched to second-line therapy may have had suboptimal adherence to their first-line regimens and may be less adherent than those who have remained on first line. This, in addition to the higher pill burden and more complex dosing intervals of the available second-line regimen, could explain the lower proportion of patients

on second-line therapy who were virologically suppressed at each duration of follow-up.

Our finding that LTF is increasing with calendar time is in line with previous studies from resource-limited settings [7,39], which we ascribe to rapidly increasing patient numbers and resultant pressure under which services are operating, and the declining ability of services to actively trace patients who miss appointments.

A number of tracing studies [40–42] done in southern Africa have demonstrated that upwards of a quarter of patients LTF have died. Our analysis confirms high mortality in those lost to follow-up (33%). We also found that the probability of death amongst those LTF is related to the duration on ART prior to being lost. In order to understand the long-term effectiveness of ART in southern Africa, it will be necessary to establish well supported sentinel cohorts in which ascertainment of both laboratory and vital status outcomes is prioritized.

Initial positive reports of patient outcomes on ART in resource-poor settings were interpreted by many as demonstration projects, made possible by the investment of additional resources that might not be sustained over time and when scaled up. Khayelitsha is, however, one of the most difficult areas in the Western Cape Province in which to provide health services due to chronic under-resourcing and an enormous burden of infectious and noncommunicable disease. The Khayelitsha ART service has been predominantly staffed and run by government health services for the past few years and has faced the same stresses, understaffing and crises faced by the health services in the area in general. When compared with routine reporting across the entire province [7], or other cohort studies in the province [43], Khayelitsha is an averagely performing subdistrict. It is, thus, likely that our findings are generalizable to other low and middle-income countries, but aspects may not apply to programmes without virological monitoring. In the first group of patients accessing ART in Botswana followed up to 5 years [8], cumulative mortality and LTF at 5 years were 21.8 and 21.0% compared with 15.5 and 23.4% in our study prior to incorporating death registry data. Available viral load suppression measures in the Botswana study were comparable or higher than in our study at each duration on ART. In a Senegalese cohort, cumulative mortality at 5 years was 24.6% in a cohort with very low reported LTF [44].

This study has a number of limitations. First, although the level of ascertainment of deaths through data-linkage with national vital statistics may be an improvement on what is feasible in many parts of southern Africa, the sensitivity of the record-linkage was only 90%, indicating residual underascertainment of a small proportion of deaths. Although we do not consider that there is any systematic bias introduced by patients who do and do not have recorded civil identification numbers, the lower availability of this linkage field for patients starting ART in the first few years of the cohort could have introduced a bias. Second, laboratory outcomes are limited to measures that were available, and patients without tests available or who were alive but no longer in care might have altered these findings had it been possible to test them. The lack of detailed exposure data impeded some of the explorations such as the association between PMTCT interventions and subsequent virological failure on HAART, in which the inclusion of NVP in the PMTCT intervention was not known. Finally, the absence of resistance data in patients who were failing virologically limited our ability to explore the effect of delays in switching therapy on future treatment options.

At a time when there is uncertainty about continued and increased direct bilateral and multilateral funding of ART-specific interventions in countries with limited resources, these findings provide considerable reassurance that the benefits of ART in these settings are sustained. Many of the early innovations to support patient adherence have endured the rapid scale-up in patient enrolment and are today standard of care in Khayelitsha and beyond. The scale-up has itself led to further health service developments such as task shifting to nurse-managed clinical care. This study has demonstrated substantial and durable clinical benefits for those able to access the intervention throughout a 7-year period.

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Webtable 1. Linkages to the death register in patients lost to follow-up.

	≤2004	2005	2006	2007	Total
Patients starting ART by mid-2007					
n	1735	1641	2087	939	6402
Patients with valid recorded civil identification numbers					
n (% of total)	689 (39.7%)	966 (58.9%)	1332 (63.8%)	663 (70.6%)	3650 (57.0%)
Patients lost to follow-up					
Lost in first year on ART - n (% of total lost)	33 (19.3%)	92 (48.9%)	204 (90.7%)	43 (100%)	372 (59.2%)
Lost between 1 and 5 years on ART - n (% of total lost)	138 (80.7%)	96 (51.1%)	21 (9.3%)	0 (0.0%)	256 (40.8%)
Total lost - n (% of total started)	171 (9.9%)	188 (11.5%)	225 (10.8%)	43 (4.6%)	628 (9.8%)
Patients lost to follow-up with civil ID numbers					
Lost in first year on ART - n (% of lost)	4 (12.1%)	48 (52.2%)	97 (47.5%)	28 (65.1%)	177 (47.6%)
Lost between 1 and 5 years on ART - n (% of lost)	51 (37.0%)	55 (57.3%)	9 (42.9%)	0	116 (45.3%)
Total - n (% of lost)	55 (32.2%)	103 (54.8%)	106 (47.1%)	28 (65.1%)	293 (46.7%)
Weights used in the corrected mortality estimates					
For patients lost in first year on ART	8.3	1.9	2.1	1.5	
For patients lost from 1 to 3 years	2.9	1.7	2.3		
For patients lost from 3 to 5 years	1.9				
Deaths in patients lost to follow-up with ID numbers					
Lost in first year on ART - n (% of lost)	3 (75.0%)	19 (39.6%)	38 (39.2%)	15 (53.6%)	75 (42.4%)
Lost between 1 and 5 years on ART -n (% of lost)	6 (11.8%)	13 (23.6%)	1 (11.1%)	0	21 (18.1%)
Total - n (% of lost)	9 (16.4%)	32 (31.1%)	39 (36.8%)	15 (53.6%)	96 (32.8%)

ART, antiretroviral therapy; ID, identification.