Does most early mortality in patients on ART occur in care or lost to follow-up? Evidence from the Themba Lethu Clinic, South Africa

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INTRODUCTION

In resource-limited settings, one-year mortality on antiretroviral therapy (ART) is about 10% with lower mortality thereafter[1–3]. However, record-keeping and reporting of mortality from observational cohorts rarely allows differentiating mortality in care or among patients lost to follow-up (LTF).

We compared mortality among patients in care and LTF after treatment initiation and assess the sensitivity of estimates to different definitions of loss to follow up.

METHODS

Study population:

- Non-pregnant ART-naïve adults with valid national IDs initiating first-line ART April 2004–May 2012 at Themba Lethu Clinic in Johannesburg, South Africa
- Mortality ascertained from the national death registry
- Dataset closed in December 2012, six months before linkage with the registry

Study variables:

- **Exposure** was whether or not the patient was LTF after treatment initiation
- **Primary outcome** was mortality as confirmed by the national death registry
- Multiple definitions of LTF were included, ranging from ≥1 day to ≥6 months late. Patients could contribute person-time to both in care and LTF groups
- Person-time in care began when treatment started and ended at the earliest of LTF, death, transfer or dataset closure
- LTF time accrued from date of loss until restarting ART, death, or censoring

Statistical methods:

- Relation between LTF status and mortality was estimated with Cox proportional hazards models (adjusted for gender, age, CD4 count, body mass index, haemoglobin level, first-line ART regimen, ART start year, and TB co-infection)

RESULTS

- 18,483 patients initiated ART, of whom 12,222 (66.1%) had valid national IDs
- Patients followed for 43,378 person-years (py) (median 3.2 py, IQR 1.4–5.5)
- 14.6% of patients (1,784/12,222) died
- With LTF defined as ≥3 months late for a scheduled visit:
  - Nearly 76% (1,350/1,784) of all deaths were considered to be in care
  - Being lost accounted for a minority of overall deaths (population attributable fraction: 14.3%, 95% CI: 12.1–16.6)
  - Mortality rates were higher in patients lost (85.4 deaths/1,000 py, 95% CI: 77.7–93.8) than in care (35.3 deaths/1,000 py, 95% CI: 33.4–37.2)
  - In adjusted analyses, individuals lost had 2.05 times higher mortality than those in care (HR: 2.05; 1.81–2.31)
  - Varying the LTF definition from ≥1 day to ≥6 months causes the mortality rate in patients lost to decrease (Figure 1).

Table 1. Baseline characteristics

Characteristics	Exposure	Total cohort (n=12,222)
Sex	Male	4,652 (38.1%)
Age at ART Initiation (years)	Median (IQR)	37.2 [31.8–43.8]
ART guideline initiated on	2004 ART Guideline	8,463 (69.2%)
	2010 ART Guideline	3,759 (30.8%)
CD4 at ART Initiation	Median (IQR)	98 [37–173]
(cells/mm^3)	0-50	3,434 (28.1%)
	51-100	2,131 (17.4%)
	101-200	3,641 (29.8%)
	201-350	1,562 (12.8%)
	>350	196 (1.6%)
	Missing	1,258 (10.3%)
Drug in first-line ART	TDF+3TC/EMT+EFV	3,076 (25.2%)
Regimen	AZT+3TC+EFV	284 (2.3%)
	d4T+3TC+EFV	7,697 (63.0%)
	Other	1,165 (9.5%)
Tuberculosis at Initiation	Yes	1,800 (14.7%)
Body mass index (kg/m^2)	Median (IQR)	21.8 [19.2–25.1]
Haemoglobin at Initiation	Non-Anaemia	2,916 (23.9%)
	Mild Anaemia	4,635 (37.9%)
	Moderate Anaemia	2,684 (22.0%)
	Severe Anaemia	1,093 (8.9%)
	Missing	894 (7.3%)

Figure 1: Mortality rates among patients in care and lost to follow-up (LTF)

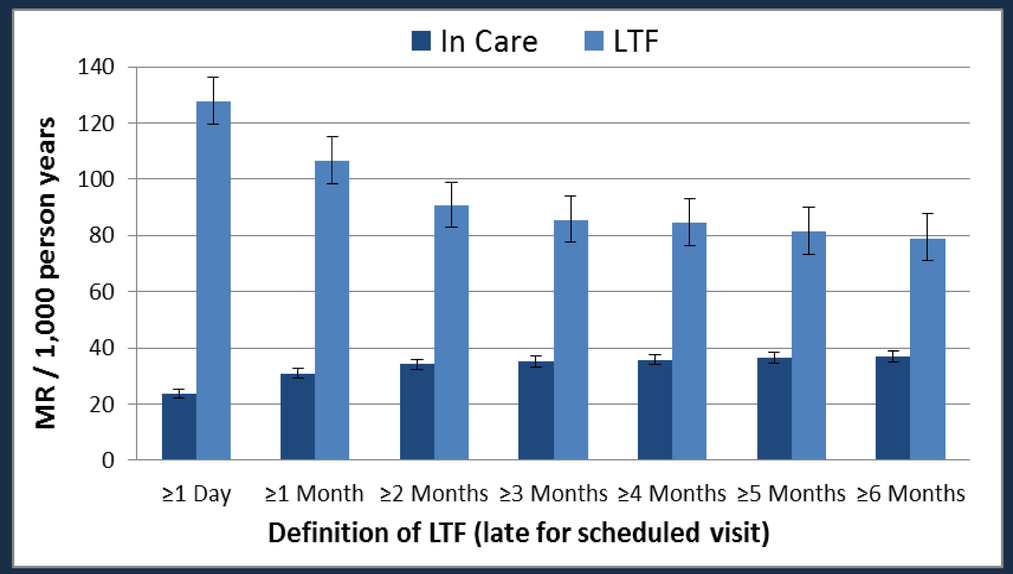

Table 2. Mortality rates among 12,222 adults in care and lost to follow-up at the Themba Lethu clinic in Johannesburg, South Africa

Definition of loss	Exposure group	N	Person time (years)	Deaths (%)	MR/1,000 py (95% CI)	MR difference: deaths /1,000 py (95% CI)	1st year after ART initiation (months 0-11) MR/1,000 py (95% CI)	1st year after ART initiation (months 0-11) MR difference: deaths /1,000 py (95% CI)	First 2 years after ART initiation (months 0-23) MR/1,000 py (95% CI)	First 2 years after ART initiation (months 0-23) MR difference: deaths /1,000 py (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
≥1 Day late	In Care	6,017	36,095	854 (14.2%)	23.7 (22.1-25.3)	REF	67.0 (61.9-72.4)	REF	40.8 (37.7-44.2)	REF	1	1
	LTF	6,205	7,283	930 (15.0%)	127.7 (119.7-136.2)	104.0 (95.7-112.4)	321.9 (291.5-355.6)	255.0 (222.5-287.4)	226.4 (207.9-246.5)	185.6 (166.0-205.1)	2.75 (2.49-3.04)	3.29 (2.93-3.68)
≥1 Month late	In Care	9,042	37,503	1,158 (12.8%)	30.9 (29.1-32.7)	REF	83.0 (77.5-88.9)	REF	52.1 (48.7-55.8)	REF	1	1
	LTF	3,180	5,874	626 (19.7%)	106.6 (98.5-115.2)	75.7 (67.2-84.2)	279.0 (242.8-320.7)	196.0 (156.7-235.3)	197.6 (177.2-220.4)	145.5 (123.6-167.4)	2.23 (2.02-2.47)	2.57 (2.30-2.88)
≥3 Months late	In Care	9,957	38,296	1,350 (13.6%)	35.3 (33.4-37.2)	REF	91.9 (86.2-98.0)	REF	58.9 (55.3-62.8)	REF	1	1
	LTF	2,265	5,082	434 (19.2%)	85.4 (77.7-93.8)	50.2 (41.9-58.4)	200.7 (162.0-248.5)	108.8 (65.5-152.1)	157.1 (136.3-181.0)	98.1 (75.5-120.7)	1.80 (1.61-2.01)	2.05 (1.81-2.31)
≥6 Months late	In Care	10,307	38,981	1,437 (13.9%)	36.9 (35.0-38.8)	REF	94.9 (89.2-101.1)	REF	61.6 (57.9-65.5)	REF	1	1
	LTF	1,915	4,397	347 (18.1%)	78.9 (71.0-87.7)	42.1 (33.5-50.6)	164.0 (115.3-233.2)	69.0 (11.0-127.1)	145.3 (122.0-173.1)	83.7 (58.1-109.4)	1.64 (1.46-1.85)	1.83 (1.60-2.08)
	Total	**12,222**	**43,378**	**1,784 (14.6%)**	**41.1 (39.3-43.1)**	**N/A**	**96.2 (90.4-102.3)**	**N/A**	**65.8 (62.1-69.7)**	**N/A**	**N/A**	**N/A**

DISCUSSION

- Our findings indicate that while mortality rates in patients LTF are much higher than in care, most ART-related mortality occurs in care
- The greatest reductions in ART-related mortality may therefore be achieved through interventions that target risk factors for death among patients currently in care.

- Our analysis shows relatively stable estimates of loss and subsequent mortality rates when the definition of loss is varied between 2 and 6 months late for a scheduled visit.
- To improve patient management and recall efforts, it may therefore be preferable to use a shorter definition of loss such as ≥2 months late for a scheduled visit.

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