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Using Vital Registration Data to Update Mortality among Patients Lost to Follow-up from ART Programs: Evidence from the Themba Lethu Clinic, South Africa

Matthew P. Fox^{1,2}, Alana Brennan^{1,2}, Mhairi Maskew^{3,4}, Patrick MacPhail^{3,4}, and Ian Sanne^{3,4}

¹ Center for Global Health and Development, Boston University, Boston MA, USA

² Health Economics and Epidemiology Research Office, University of the Witwatersrand, Johannesburg, South Africa

³ Right to Care, Johannesburg, South Africa

⁴ Clinical HIV Research Unit, Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa

Summary

Objective—To estimate the rates of mortality in patients lost to follow up (LTFU) from a large urban public sector HIV clinic in South Africa.

Methods—We compared vital status using the clinic's database to vital status verified against the Vital Registration system at the South African Department of Home Affairs. We compared rates of mortality before and after updating mortality data. Predictors of mortality were estimated using Kaplan-Meier curves and proportional hazard regression.

Results—Of the 7,097 total patients who initiated HAART at LTC by October 1st, 2008 and had an ID number, 6205 were included. 2453 patients (21%) were LTFU, of whom 1037 (42.3%) could be included in the analysis. After matching to the vital registration system, mortality more than doubled from 4.2% (258/6205) to 10.0% (623/6205). By life-table analysis the probability of survival amongst those LTFU was 69.2% (95% CI: 66.3%–72%), 64.2% (95% CI: 61%–67%) and 58.7% (95% CI: 55%–62%) by years 1, 2 and 3 since being lost, respectively. Those at highest risk of death after being lost were patients with a history of tuberculosis, CD4 count <100 cells/ μ L, BMI <17.5, hemoglobin <10 and on <6 months of treatment.

Conclusion—Mortality was substantially underestimated among patients lost from a South African HIV treatment program despite limited active tracing. Linking to vital registration systems can provide more accurate assessments of program effectiveness and target lost patients most at risk for mortality.

Keywords

human immunodeficiency virus; antiretroviral therapy; mortality; loss to follow up; risk factors; South Africa; sub-Saharan Africa

INTRODUCTION

As access to antiretroviral therapy (ART) has grown exponentially in low and middle income countries since 2004 (Sepulveda et al. 2007; WHO 2005a,b, 2008), attention has shifted from the immediate need to get patients into care, to the long-term challenges of keeping patients in care and on treatment. While virologic outcomes on ART in low income countries are positive (Egger et al. 2002; Coetzee et al. 2004; Laurent et al. 2005; Ivers et al. 2005; Lawn et al. 2005) and similar to that of developed areas (Keiser et al. 2008), losses from HIV treatment programs in low income countries have been reported to be nearly 40% by two years after ART initiation (Rosen et al. 2007). These losses continue to reduce the ability to assess the overall effectiveness of HIV treatment programs.

Few representative studies exist to inform us on the mortality rates of patients who are lost from HIV care. In some cases, being lost means a patient has found care elsewhere, while in others, particularly in rural areas, patients may have few other options for seeking ART resulting in discontinuation of care and treatment. It has been reported that patients who have been reported as lost and do not seek care elsewhere are likely to die within one year of leaving care (Mocroft et al. 1997; Badri et al. 2006; Morgan et al. 2002). According to a recent systematic review and meta-analysis of outcomes of patients lost to HIV care and treatment programs, 20–60% of patients who could be traced had died (Brinkhof et al. 2009).

Studies of the effectiveness of ART programs as well as monitoring and evaluation statistics typically separate out death and lost to follow up (LTFU). Often the majority of reported attrition from ART programs is in the LTFU category as tracing patients who are lost to follow up is both difficult and requires using limited resources for tracing. However, in order to be able to determine how effective the global ART scale up is at reducing mortality, it is essential to have accurate data on patient outcomes after leaving care.

One method of reducing the number of missed deaths in ARV treatment programs is through linking with national vital registration systems. While vital registration systems in low and middle income countries often have poor sensitivity, in South Africa, where the largest number of HIV positive patients in the world are living, the National Vital Registration system has been demonstrated to detect nearly 90% of all adult deaths (Statistics SA 2005; Dorrrington et al. 2001; Timaeus et al. 2002). Still, few HIV treatment programs even within South Africa have the resources to be able to devote to investigating the outcomes among patients lost. Thus to better understand vital status outcomes among patients lost from HIV treatment programs as well as what predicts mortality among those lost, we analyzed data from a large urban public sector HIV clinic in South Africa where vital status had been verified against the Vital Registration system at the South African Department of Home Affairs.

METHODS

Study Site

The study was conducted at Themba Lethu Clinic (TLC) in Johannesburg, South Africa. TLC is a public sector ART clinic that began large scale provision of ART in April 2004 as part of the South African government's Comprehensive Care Management and Treatment of HIV (CCMT) program. The clinic also receives funding from Right to Care, a South African NGO supporting HIV treatment through PEPFAR. The clinic is the largest in South Africa, with more than 20,000 patients ever initiated on ART, more than 12,000 patients actively on ART and thousands more in pre-ART care. Currently the clinic staff provide upwards of 500

consultations per day with care provided according to the guidelines from the South African National Department of Health (NDH 2004).

Use of Themba Lethu Clinic data and linkage of this data with the Department of Home Affairs Vital Registration system was approved by the Human Research Ethics Committee of the University of the Witwatersrand and by the Ethics Board of the University of Cape Town. Approval for analysis of the data in a de-identified manner was granted by the Institutional Review Board of Boston University.

Data Sources

Themba Lethu Clinic—Themba Lethu Clinic uses a real time data capturing system called TherapyEdge-HIV™ in which data on all patient encounters (including scheduling information, demographic indicators clinical conditions, laboratory results and patient outcomes) is captured at the time of the encounter by a clinician or member of the clinic staff. At enrollment South African citizens are asked to give their South African National Identification number, though care is provided to all patients including those who do not have or do not wish to provide one.

We defined LTFU as having missed a clinic appointment (*e.g.* clinical assessment, ARV pickup, counselor visit, etc.) by at least three months after the scheduled visit date. The cumulative incidence of LTFU by Kaplan-Meier analysis was 13.7% during the first year on ART and 21.7% after three years on ART. Since 2007, TLC has had a limited initiative to actively trace those LTFU in order to improve overall retention in care. At enrollment, patients are asked if they are willing to be contacted should they leave care, and to provide an address, a phone number and a friend or relative's phone number. Close to 95% of patients participate in this program. If a patient becomes lost, counselors attempt to contact the patient and return them to care typically by phone and if not reachable via phone then by home visit. Patients found to be receiving care elsewhere are updated as having been transferred and those found to have died have their vital status updated in the database. The objective of the program is to contact as many lost patients as possible, however as funding is limited and the clinic is large, not all patients can be contacted. In addition, patients lost who were contacted but could not be reengaged in care would be listed as lost in the database even if they later went on to die.

As of October 2008, a total of 11,694 patients were initiated on ART at TLC, of whom 7,097 (60.7%) provided a legitimate South African ID number that could be linked to the death registry. Often, in the early years of the clinic's operation, ID numbers were not collected. In some cases this was simply the practice of those enrolling patients, while in others it was because the clinic serves a diverse population of patients, some of whom are not from South Africa who would not have a national ID number. Patients without an ID number were similar to those included in the analysis in terms of mean baseline CD4 count (104.5 vs. 104.8), hemoglobin (11.3 vs. 11.6), and BMI (21.3 vs. 22.5). There were also no significant differences in age, sex or race between the two groups.

Of the 7,097 patients, we excluded all those who initiated ART prior to the government roll out on April 1st 2004 (N=184) and all patients who transferred out of care at TLC (N=320 of whom 8% died) as their LTFU status could not be determined. In addition, we excluded all women who had incident pregnancies (N=316) because we found an inverse association between incident pregnancy and LTFU (HR .42; 95% CI 0.29–0.60), largely because the clinic refers pregnant women to another clinic for care during their pregnancy. Finally, we excluded all patients who were LTFU less than 6 months prior to the linkage (N=72), as they may not have been included in the registry if they had died due to delays in reporting. This left 6,205 subjects who were eligible for the current analysis. At the time of the linkage 21%

(N=2,453) of all HAART patients were LTFU, of whom 42.3% (N=1,037) gave a legitimate identification number and were included in the analysis.

National Death Registry—In South Africa, all deaths must be reported to the Department of Home Affairs (DHA) for issuance of a death certificate. While no registry is 100% accurate, in South Africa, the National Death registry is fairly comprehensive. Statistics South Africa estimates that 90% of all adult deaths are captured through this system (Statistics SA 2005; Dorrington et al. 2001; Timaeus et al. 2002). In Free State province, over 80% of all deaths identified from their ART program were found through the registry rather than through patient files (Fairall et al. 2008).

To assist in the identification of patients lost from HIV care, vital status of all patients in the TLC dataset who began ART between April 2004 and September 2008 was verified through the registry by a member of the DHA with ethics approval to conduct the linkage. As South African ID numbers require certain digits to take on specific values, only legitimate ID numbers were validated. When a match was found the death was recorded along with a date of death. The linked file was returned and used to update the clinic records and the data was then de-identified for analysis.

We note that there is a delay in reporting to and updating the vital registration data thus some patients listed as not having died in the current analysis may have died but were not yet reported to the registration system. To account for this, as noted above, all patients who were LTFU less than 6 months prior to the linkage were excluded from the analysis.

Statistical Methods

We calculated the overall mortality in the treatment program both before and after linking with the vital registration system. We present each as simple proportions and 95% confidence intervals. We then conducted a similar analysis limited to only patients who were lost from the TLC ART program. We looked for crude differences between groups using proportional hazards regression. We used life-table methods to calculate the proportion of patients lost who had died in the years following being lost. To look for predictors of death among those who were LTFU we calculated crude Kaplan-Meier estimates of mortality and adjusted predictors of mortality were estimated using Cox proportional hazard regression.

RESULTS

Table 1 shows characteristics of the cohort of 6,205 patients stratified by their vital status after the linkage. Patients were enrolled fairly evenly over the roughly four years of follow up. The majority of patients were black (94.7%), female (64.1%), between 30–40 years of age (48.7%) and on the standard first line regimen of stavudine (D4T), lamivudine (3TC) and efavirenz (EFV). Of the 6,205 eligible subjects, 258 (4.2%) were known to have died before updating vital status and 1,037 (16.7%) were LTFU.

Vital Status Outcomes

Table 2 shows the mortality data within the clinic before and after updating vital status. In total 4.2% of patients were known to have died according to the clinic records (258/6,205). After updating the clinic records by matching to the vital registration system, mortality went up to 10.0% (623/6,205), more than double. Using product-limit estimates, the cumulative one year and three year mortality estimates after the linkage were 7.8% and 11.7% respectively.

Among those lost from the clinic, after the linkage 333 patients (32.1%; 95% CI: 29.3%–35.0%) were known to have died. As would be expected, the rate of death among those LTFU increased with duration since being lost, with over 65% of those lost in 2004 having died, while less than 30% of those lost in 2007 were deceased (Figure 1). Regardless of the calendar year in which patients became lost, more than 75% of all deaths occurred within one year of being lost and nearly 95% occurred within two years. By life table analysis (Table 3) we estimate that the cumulative probability of survival amongst those LTFU was 69.2% (95% CI: 66.3%–72%) by one year since being lost compared to 64.2% (95% CI: 61%–67%) and 58.7% (95% CI: 55%–62%) by years two and three, respectively.

Predictors of death among those lost

Figure 2 shows crude Kaplan-Meier survival curves in the year after being lost from HIV treatment. Mean follow-up time was 253 days (range 0–365). Of the 1,037 subjects included in this analysis, 333 (32.1%) died. Fewer survived of older patients, those with more severe disease progression and those with shorter duration on treatment prior to being lost (logrank p -value < 0.0001 for all). In adjusted analyses (Table 4), the strongest predictors of mortality after being lost were having a low CD4 count before being lost (≤ 100 vs. > 200 HR 3.38; 95% CI 2.27–5.03) and having a BMI <17.5 before being lost (HR 2.35; 95% CI 1.76–3.14).

DISCUSSION

Understanding the impact of losses from HIV treatment programs is critical to accurately evaluating their overall success. In some HIV treatment programs, LTFU may constitute the largest proportion of overall program attrition (Rosen et al. 2007). In our study, ascertainment of mortality was strongly underestimated in our clinic even though limited active tracing does exist. After matching clinic data with the vital registration system mortality more than double from 4.2% to 10.0%. While this increase is large, other programs without active tracing programs have estimated that their mortality increased as much as five-fold after adjusting for the high rate of death amongst those lost (Geng et al. 2008a).

Our study confirms, in a well defined population, the suspicion that there is high mortality amongst those lost from HIV treatment programs in South Africa. We found that the probability of death among those lost to follow-up was nearly 30% at the end of one year. It is encouraging, however, to see that the rate of death in the first year after being lost has steadily fallen since 2004 (test for trend $p = 0.0002$). While this overall high mortality rate among those lost means that many who are lost are likely not seeking care from another provider, others may be, particularly as more options for care become available. In a recent systematic review, Brinkhof et al. (2009) estimated that among those lost whose vital status could be determined mortality was as high as 40%, 10% higher than our estimate. Because our study included all patients whose national ID number we had, our study is likely more representative of the clinic population than would be achieved by attempting to contact patients. In addition, as their data was a systematic review it contained results from much earlier in the experience with ART scale up and therefore may reflect higher mortality associated with more limited access to care and fewer options for transferring to another site.

Appropriately evaluating treatment programs means assessing treatment outcomes for all patients. Typically analyses of ART program effectiveness report on both mortality and LTFU because the two are closely linked, but many of those who are lost will have died and are therefore misclassified. It has previously been shown that failure to determine the outcomes in patients lost can cause dramatic underestimation of overall mortality. In a cohort in Botswana missing deaths among those LTFU caused overestimating of one year

survival rates by nearly 10% (Bisson et al. 2008). Despite this, as resources targeted for tracing patients who are lost are limited, outcome assessment remains poor.

A 2007 review concluded that in Africa only South Africa, Mauritius and the Seychelles have well-functioning vital registration systems (Setel et al. 2007). Outside of these areas, an alternative proposed solution to the problem of poor outcome assessment is to trace randomly sampled subsets of the population and use estimates from the subset whose vital status can be traced to adjust overall estimates of mortality in the cohort (Yiannoutsos et al. 2008; Geng et al. 2008b). Another approach uses a nomogram approach to adjust overall mortality (Egger et al. 2009). When no viable vital registration system exists but resources are available to contact a sample of patients, this approach is likely an improvement over crude approaches which ignore LTFU. However, our study demonstrates that even approaches that sample patients to determine their vital status likely suffer from some bias as they miss patients who cannot be contacted and may miss deaths among patients who go on to die after the sampling.

Despite the benefits of using statistical approaches to adjust for deaths among those lost, this approach is not preferable to directly identifying the vital status of those LTFU. Programs with active tracing have been shown to have substantially lower rates of death than those without (Keiser et al. 2008). This approach has the added advantage of being able to bring patients back into care and potentially reduce the overall mortality rate. Still when not possible, our results show that matching with vital registration systems can be successfully implemented to better estimate the total mortality of patients in ART programs.

While all patients lost from care are at increased risk for mortality, identifying patients at highest risk for dying after leaving care is of critical importance. In our analysis, those at highest risk of death after being LTFU were predominately those who were sickest when leaving care (low CD4 count, BMI and hemoglobin levels before leaving care) and those on treatment for < 6 months prior to being lost. In cases where limited resources exist for getting patients back into care, these sicker patients should be prioritized for tracing and returned to care.

Our findings must be interpreted in light of their limitations. First, since it is not mandatory for patients to provide a National Identification number when registering for treatment at the clinic we were not able to verify the outcome status of all patients. The clinic in which the study was conducted does not turn away patients regardless of whether or not they have a National ID number. Patients without an ID number could not be included in the analysis and may have been more likely to have died than patients included in the study. If so, our estimates of updated mortality would likely be underestimates. In addition, because stigma still exists around HIV/AIDS some patients may provide a fake identification number for fear of being identified as being HIV positive or of being turned away. Given this, despite dramatically increasing our overall mortality rate to more accurately reflect overall programmatic impact, we are still likely underestimating the true mortality rate amongst those LTFU at the clinic.

In conclusion, we found that mortality was substantially underestimated among patients lost to follow up in an HIV treatment program in Johannesburg, South Africa despite an active tracing program to return patients lost to care. Linking to the national vital registration system proved to be a practical method to more accurately represent mortality in the cohort. Linking to vital registration systems, when feasible can provide a means to more accurately assess the effectiveness of a program and target LTFU patients most at risk for mortality.

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Figure 1. Proportion of subjects who were determined to be lost by the clinic who were confirmed dead in the South African Vital Registration database by year lost from the clinic*

* Excludes those lost in 2008 (N=173) as subjects lost in 2008 would not all have completed a potential one year since being lost

Figure 2. Crude Kaplan-Meier Survival Curves for Death by One Year since Time of Being Lost among Patients on HIV Treatment at the Themba Lethu HIV Clinic*

* Stratified by a) year lost to follow up; b) age at being lost; c) last CD4 count before being lost d) last BMI before being lost e) last Hb before being lost and f) months on ART before being lost. Log rank p-value < 0.0001 for all.

Table 1

Demographic and Clinical Characteristics of the Eligible 6,205 patients on ART* at the Themba Lethu Clinic in Johannesburg, South Africa from April 2004–September 2008 by Vital Status

Variable	Exposure	Died	Alive	Hazard Ratio of Death (95% CI)
Sex	Female	398 (10.0%)	3578 (90.0%)	Reference
	Male	278 (12.5%)	1951 (87.5%)	1.25 (1.08–1.44)
Race is black	No	41 (12.5%)	286 (87.5%)	Reference
	Yes	635 (10.8%)	5243 (89.2%)	0.86 (0.64–1.16)
Year of initiation on first line	2004	132 (13.8%)	826 (86.2%)	Reference
	2005	195 (14.0%)	1199 (86.0%)	1.02 (0.83–1.25)
	2006	170 (11.2%)	1342 (88.8%)	0.82 (0.66–1.01)
	2007	117 (9.6%)	1103 (90.4%)	0.70 (0.55–0.88)
	2008	62 (5.5%)	1058 (94.5%)	0.40 (0.30–0.54)
Regimen at ART* initiation	d4T_3TC_EFV	593 (11.9%)	4376 (88.1%)	Reference
	d4T_3TC_NVP	29 (6.3%)	431 (93.7%)	0.53 (0.37–0.76)
	Other	54 (7.0%)	722 (93.0%)	0.58 (0.45–0.76)
Baseline WHO Stage	Stage I	161 (8.4%)	1747 (91.6%)	Reference
	Stage II	67 (9.8%)	614 (90.2%)	1.17 (0.89–1.53)
	Stage III	172 (13.1%)	1139 (86.9%)	1.55 (1.27–1.90)
	Stage IV	82 (18.9%)	351 (81.1%)	2.24 (1.76–2.87)
Baseline CD4	0–50	310 (16.9%)	1519 (83.1%)	Reference
	51–100	127 (11.5%)	975 (88.5%)	0.68 (0.56–0.82)
	101–200	129 (7.1%)	1691 (92.9%)	0.42 (0.34–0.51)
	> 200	32 (5.5%)	547 (94.5%)	0.33 (0.23–0.46)
Last CD4 count [#]	0–50	266 (47.1%)	299 (52.9%)	Reference
	51–100	127 (29.8%)	299 (70.2%)	0.63 (0.53–0.75)
	101–200	158 (13.0%)	1053 (87.0%)	0.28 (0.23–0.33)
	>200	117 (2.9%)	3850 (97.1%)	0.063 (0.05–0.08)
History of TB [^]	No	605 (10.9%)	4930 (89.1%)	Reference
	Yes	71 (10.6%)	599 (89.4%)	0.97 (0.77–1.22)
Last viral load [#]	< 100	166 (3.8%)	4209 (96.2%)	Reference
	100–10,000	39 (9.8%)	359 (90.2%)	2.58 (1.85–3.60)
	> 10,000	101 (23.5%)	329 (76.5%)	6.19 (4.94–7.77)
Age at initiation	18–29.9	116 (9.7%)	1080 (90.3%)	Reference
	30–39.9	311 (10.3%)	2711 (89.7%)	1.06 (0.87–1.30)
	40–49.9	180 (12.2%)	1291 (87.8%)	1.26 (1.01–1.57)
	50+	69 (13.4%)	447 (86.6%)	1.38 (1.04–1.82)
Last BMI < 17.5 [#]	No	398 (7.8%)	4702 (92.2%)	Reference
	Yes	155 (47.5%)	171 (52.5%)	6.09 (5.25–7.06)
Last HB <10 [#]	No	439 (7.9%)	5119 (92.1%)	Reference
	Yes	222 (39.3%)	343 (60.7%)	4.97 (4.34–5.70)
Time on ART*	0–3mos.	323 (33.5%)	641 (66.5%)	Reference

Variable	Exposure	Died	Alive	Hazard Ratio of Death (95% CI)
	3–6mos.	110 (20.2%)	434 (79.8%)	0.60 (0.50–0.73)
	6–12mos.	107 (14.3%)	642 (85.7%)	0.43 (0.35–0.52)
	>=12mos.	132 (3.3%)	3810 (96.7%)	0.10 (0.08–0.12)

* ART = antiretroviral therapy, BMI = Body Mass Index

^ Tuberculosis before initiation of ART

For patients who died or were lost to follow up, this was their last value before leaving care. For those who are still in care this was their last visit overall

Table 2

Vital Status Outcomes among ART[^] Patients Lost to Follow-up from the Themba Lethu Clinic, Johannesburg, South Africa *

Themba Lethu Clinic Records	Vital Registration System		Total
	Registered as died	Not registered as having died	
Died	230	28	258
LTFU	333	704	1037
Alive and in care	60	4850	4910
Total	623	5582	6205
Performance	% (95% CI) [^]		N/Total
Mortality before updating	4.2% (3.7%–4.7%)		258/6205
Mortality after updating	10.0% (9.3%–10.8%)		623/6205
Mortality among LTFU after updating	32.1% (29.3%–35.0%)		333/1037

* Data was validated against South Africa's Department of Home Affairs Vital Registration System

[^] ART = antiretroviral therapy, CI = confidence interval, LTFU = lost to follow up

Table 3

Life Table Survival Estimates Up to 36 Months since Being Lost among Patients on HIV Treatment at the Themba Lethu HIV Clinic

Interval (months)	Number Failed	Number Censored	Sample Size	Conditional Probability of Failure	Survival	95% Confidence Interval
0–2.9	248	0	1037.0	0.24	1	1
3–5.9	39	4	787.0	0.05	0.76	(0.73–0.79)
6–8.9	30	99	696.5	0.04	0.72	(0.70–0.75)
9–11.9	16	77	578.5	0.03	0.69	(0.66–0.72)
12–17.9	22	100	474.0	0.05	0.67	(0.64–0.70)
18–23.9	19	98	353.0	0.05	0.64	(0.61–0.67)
24–29.9	8	77	246.5	0.03	0.61	(0.57–0.64)
30–35.9	4	96	152.0	0.03	0.59	(0.55–0.62)
36	0	100	50.0	0.00	0.57	(0.54–0.61)

Table 4

Crude and Adjusted Hazard Ratios of Mortality for the 1,037 Patients Lost from an HIV Treatment Program at the Themba Lethu Clinic, Johannesburg, South Africa*

Variable	Crude Model(95% CI [^])	Adjusted Model ^{**} (95% CI [^])
Age at time of being lost		
≤ 40	1.0	1.0
> 40	1.67 (1.34–2.08)	1.43 (1.10–1.85)
Last CD4 before being lost		
> 200	1.0	1.0
100–200	0.74 (0.57–0.96)	1.80 (1.20–2.70)
0–100	3.83 (3.06–4.79)	3.38 (2.27–5.03)
History of tuberculosis		
No	1.0	1.0
Yes	1.31 (0.98–1.74)	1.29 (0.93–1.79)
Sex		
Male	1.0	1.0
Female	0.78 (0.63–0.97)	1.07 (0.83–1.38)
Last BMI[^] before being lost		
≥ 17.5	1.0	1.0
< 17.5	3.69 (2.82–4.83)	2.35 (1.76–3.14)
Last HB before being lost		
≥ 10.0	1.0	1.0
< 10.0	2.56 (2.03–3.23)	1.39 (1.04–1.85)
Year lost from care		
2004	1.0	1.0
2005	1.52 (1.21–1.91)	0.85 (0.48–1.52)
2006	0.71 (0.55–0.92)	0.62 (0.34–1.13)
2007	0.81 (0.63–1.03)	0.81 (0.45–1.47)
2008	0.94 (0.69–1.27)	0.96 (0.52–1.78)
Months on ART before LTFU		
≥12 months	1.0	1.0
6–12 months	0.82 (0.61–1.11)	1.38 (0.90–2.11)
0–6 months	2.34 (1.86–2.94)	1.52 (1.05–2.21)

* Mortality data comes from South Africa's Department of Home Affairs Vital Registration System

** Adjusted for all other variables in the model using Cox Proportional Hazards regression

[^] CI = Confidence interval, BMI = Body Mass Index