

Title: Estimating the mortality risk correcting for high loss to follow-up among female sex workers with HIV in Durban, South Africa, 2018-2021

Running title: Mortality among female sex workers

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Abstract

Purpose: This study assesses risk factors of loss to follow-up (LTFU) and estimates mortality risk among female sex workers (FSW) with HIV in Durban, South Africa, in 2018-2021.

Methods: We used data from the *Siyaphambili* trial, which evaluated strategies for improved viral suppression. FSW with HIV aged ≥ 18 years with viral load ≥ 50 copies/mL were followed up for 18 months. LTFU was defined as absence from study or intervention visits for 6 months. We traced LTFU participants by calling/in-person visit attempts to ascertain their vital status. We used Cox regression to determine risk factors of LTFU and inverse probability of tracing weights to correct mortality risk.

Results: Of 777 participants, 10 (1.3%) had died and 578 (74.4%) were initially LTFU. Among those LTFU, 36.3% (210/578) were traced successfully, with 6 additional deaths ascertained. Recent physical and sexual violence, and non-viral suppression were associated with increased LTFU. The unweighted and weighted 18-month mortality risks were 2.4% (95% CI: 0.8%-3.9%) and 3.7% (95% CI: 1.8%-5.9%), respectively.

Conclusions: LTFU is common among FSW with HIV in South Africa with additional investigation of vital status demonstrating under-ascertained mortality. These data suggest the need for comprehensively addressing risks for mortality among FSW.

Introduction

Female sex workers (FSW) face intersecting individual, interpersonal, and structural challenges that exacerbate risk to their health and wellbeing (1). At the macro-structural level, FSW experienced economic vulnerability, housing instability (2,3), mobility (1,4), stigma (1,5), and criminalization (1,2,5), which restrict their rights and power. In their community, FSW face violence (2,6,7) and police abuse (2). Many FSW have mental health stressors with significant risk of self-harm and suicide (2,6). Reported alcohol and substance use is prevalent (2,3,7,8). Moreover, FSW have an estimated 30 times increased risk of acquiring HIV versus other reproductive-aged women (5). Because of these multifactorial barriers, FSW with HIV often struggle to adhere to ART, remain in care, and virally suppress (9). There were an estimated 146,000 FSW in South Africa in 2021 (5), with an HIV incidence of 5 infections per 100 person-years (10) and HIV prevalence of 60% (10,11). Only 70% of FSW with HIV in South Africa were reported to be using ART (11), which indicates suboptimal care coverage and heightened risks of HIV-associated morbidity and mortality. Among people with HIV (PWH), tuberculosis (TB) and cryptococcal meningitis are major causes of AIDS-related deaths (5). A recent study conducted in multiple countries, including South Africa, reported abortions, suicides, and murders as the leading causes of death among FSW (12). However, mortality among FSW remains understudied due to the lack of methodology to comprehensively capture vital status and the reported mortality among FSW may miss a significant number of deaths due to loss to follow-up (LTFU).

High LTFU has been reported among FSW in both study and care settings. Specifically, 33% of FSW became LTFU in a 5-year HIV incidence cohort conducted in Zambia (13), and 27-55% of FSW with HIV in routine care in Côte d'Ivoire and Uganda became LTFU within 24 months (9,14). Busy work schedules (15), travel (15) or migration for sex work and

economic opportunities (4), and working on the street with unstable (15) or lack of phone ownership (9) may challenge engagement in research and HIV care. However, LTFU may mean silent transfer (i.e., the participants transfer to receive HIV care at a new facility without documentation at the previous facility), disengagement from care, or undocumented death (16–18). If PWH become disengaged from care, they may have poor ART adherence and high viral load (VL), resulting in an increased risk of mortality (19). Systematic reviews of tracing studies across Sub-Saharan Africa reported a wide range between 9-87% of LTFU PWH had actually died (19–21). Understanding the factors associated with LTFU can help program implementers identify better strategies to facilitate retention. Accounting for LTFU may improve assessments of mortality and other health outcomes, which are necessary to inform improved programs and policies.

This study aims to determine factors associated with LTFU and estimate mortality risk of FSW with an unsuppressed HIV VL in Durban, South Africa, from 2018-2021, in a context of an implementation trial.

Methods

Study setting

TB HIV Care is a non-profit organization that has implemented health service programs for FSW across multiple provinces in South Africa. This study was conducted at their Durban site. An estimated 9,300 FSW lived in Durban and the HIV prevalence was 78% (22). Approximately 40% of all FSW with HIV in Durban were virally suppressed (2,22), indicating a population at high risk of treatment failure and disengagement from care.

Study design

These analyses used data from the *Siyaphambili* study, which was a sequential multiple assignment randomized trial evaluating two interventions for improved viral suppression: a mobile van-based decentralized treatment program and a peer-led individualized case management. The methods have been previously described (23). Briefly, participants in the decentralized treatment program refilled ART every 1-3 months at the mobile clinic. The participants receiving individualized case management received peer-delivered counseling in-person twice in the first month and then once every three months, in addition to counseling via phone call every month, while separately continuing to refill ART at their regular clinic. Interviewer-administered questionnaires and laboratory testing for HIV VL and CD4 cell count were conducted at baseline and follow-up study visits at 6, 12, and 18 months.

Study population

We enrolled FSW, defined as cisgender women who reported exchanging of sex for money or goods as their primary source of income, aged ≥ 18 years, HIV diagnosed for ≥ 6 months, living in Durban, and speaking Zulu or English. Exclusion criteria included being pregnant at enrollment, planning to relocate or travel outside Durban for >3 months in the next year, being on a second-line ART regimen, and participating in an adherence club or other study. Peer case managers consecutively recruited and screened FSWs accessing services at the TB HIV Care mobile vans parked at sex work venues and from the TB HIV Care drop-in centers according to the eligibility criteria. Only participants who had VL ≥ 50 copies/mL at screening were randomized between June 22, 2018, and March 23, 2020, to receive the active intervention(s), and were included in this analysis.

Study outcomes

The participants were classified as LTFU after they were absent from any visits for ≥ 6 months for the first time. We chose 6 months because this was the planned period between study visits and encompassed multiple planned intervention delivery visits and the 90-day post-expected visit LTFU definition according to South Africa's clinical guidelines.

Death was confirmed by speaking to participants' family members or peers, or via hospital records.

Tracing

Per study protocol, peer counselors and study staff traced all participants who missed any study or intervention visits by calling and visiting their sex work venue in the community based on the provided contact information and made at least three attempts to locate the participants. Participants could re-engage at any time during the study period. All participants who did not show up at their 18-month study visit were traced using the same protocol.

This analysis treated the data of the participants who returned for any follow-up visits after meeting the 6-month LTFU definition as a "tracing sample". LTFU participants who did not return for subsequent visits were classified as "traced unsuccessfully." LTFU participants who returned for any subsequent visits were classified as "traced successfully."

Statistical analyses

The baseline characteristics stratified by initial death and LTFU status were summarized using frequency and percentages.

We used Cox regression to describe risk factors for LTFU. We built our regression model by first selecting risk factor variables from literature and mapped them to the conceptual framework for structural HIV determinants and sex work (Figure 1) (1). We built a multivariable model, including only covariates with $p\text{-value} < 0.10$ in the univariable models. We grouped participants who died with participants who were not LTFU and censored them at the time of death. The values of the time-varying variables as denoted in Figure 1 were updated if the participants completed the questionnaire during the follow-up visits, otherwise the values were carried forward. To deal with missing baseline variables, we conducted multiple imputation with chained equations (24) with 20 imputations and 20 iterations for each imputation. We estimated the hazard ratios (HR) and their corresponding 95% confidence interval (CI) separately for each imputed dataset first before combining them using Rubin's rule (25). Additionally, we assessed the impact of COVID-19 pandemic on the results by adding enrollment period to the model.

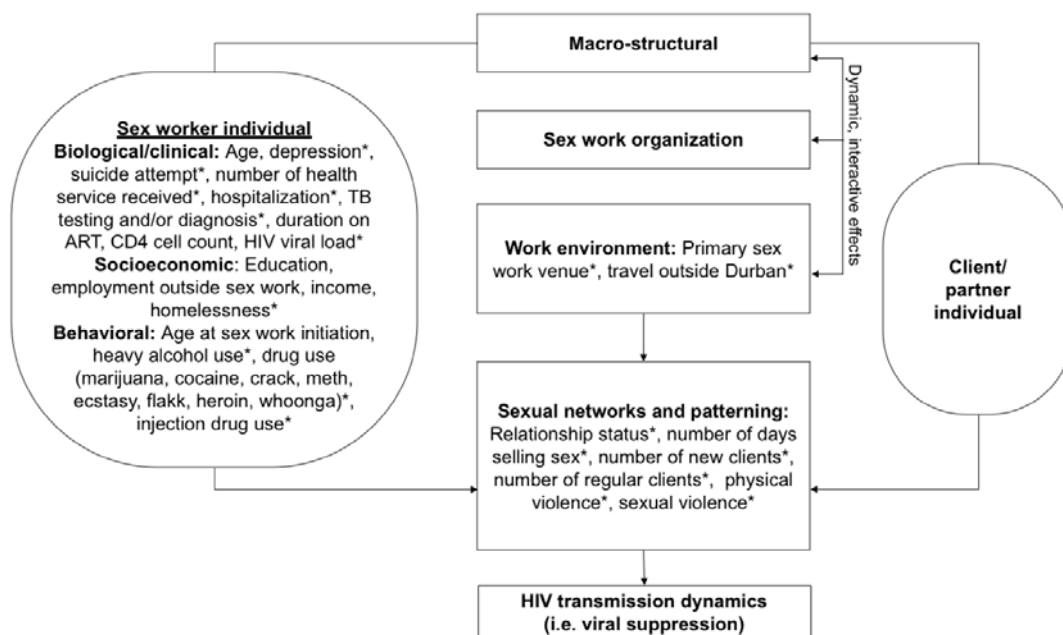


Figure 1. Observed determinants of loss to follow-up among female sex workers with HIV mapped to the conceptual framework for structural HIV determinants and sex work (1). This adapted conceptual framework was used to inform variable inclusion in the Cox regression model for describing risk factors of loss to follow-up. At the individual levels, we included demographic and socioeconomic characteristics, substance use behaviors, mental health issues, health service access, and HIV-related variables. At the psychosocial level, we included sexual patterning, history of experiencing violence, and sex work experiences. All variables were measured at baseline; time-varying variables designated with asterisk were collected at 6-month intervals during the study visits.

Note: Whoonga is a smoked street drug that often contains low-grade heroin, household products, such as detergent and rat poison, and antiretroviral medication (26).

Antiretroviral therapy, ART; tuberculosis, TB.

We estimated the mortality risk by using the complement of the Kaplan-Meier survival function in two approaches. In the unweighted approach, we included deaths captured before the participants met the 6-month LTFU definition. All participants were implicitly assigned a weight of one, allowing the outcomes of participants who remained in the study to stand in for the outcomes of those LTFU (27).

In the weighted analysis, we used inverse probability weights derived from the tracing sample, which is an approach used in several resource-limited settings to correct mortality estimates in HIV literature (16,28–37). Participants who were not LTFU were assigned a weight of one. LTFU participants who were traced unsuccessfully were assigned a weight of zero and dropped from this analysis. LTFU participants who were traced successfully were assigned a weight that was the inverse of the probability of being traced

successfully given that a participant was LTFU. Thus, we allowed the outcomes of participants who were traced successfully to stand in for the outcomes of those we could not trace. The participants were followed up from study enrollment to death, LTFU, or administrative censoring at month 18 study visit or 18 months, whichever came first. LTFU participants contributed their person-time until meeting the 6-month LTFU definition to yield the least biased result (38) (Figure S1). We estimated the 95% CI from 2000 bootstrap samples drawn with replacement. Since we attempted to trace all LTFU participants, we compared the observed baseline characteristics among the participants who were traced successfully and traced unsuccessfully using chi-squared test and Fisher's exact test to assess exchangeability assumption (28).

Since vital status could be missing not at random (39), we conducted a quantitative bias analysis to estimate a range of mortality risks (40) assuming 5-30% of LTFU participants had died within 18 months. This range overlaps 18.1-37.0% reported by studies conducted among general PWH in South Africa between 2001-2012 using 6-month LTFU definitions but linking the participants' identity to the national death registry (18,37,41-43); a more recent study conducted in 2014-2017 using 3-month LTFU definition reported 5% (44). We upweighted the deceased participants and downweighted the alive participants who were LTFU and traced successfully by respectively assigning the product of the tracing weight, the inverse of the observed probability of being deceased or alive given that the participant was LTFU, and the assumed probability of LTFU participants being deceased or alive.

Statistical analyses were conducted with R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

The study was approved by the University of the Western Cape Biomedical Research Ethics Committee in South Africa, the Johns Hopkins School of Public Health Institutional Review Board in the United States, and the eThekweni Municipality and KwaZulu-Natal Provincial Departments of Health. Eligible participants provided written informed consent. Tracing was conducted as part of the consented study activities after a missed visit.

Results

Of 777 participants, 10 (1.3%) participants had died and were not LTFU, 189 (24.3%) participants were alive and engaged in research or services, and 578 (74.4%) participants were LTFU (Figure 2). As shown in Table 1, 58.0% of the participants overall were aged 25-34 years, 80.8% had less than secondary education, 95.0% had no employment outside sex work, and 62.5% sold sex for ≥ 20 days per month. Many participants experienced homelessness (36.0%), heavy alcohol use (i.e., 5+ drinks 2+ times weekly; 42.1%), and reported illicit substance use in the past 30 days, including marijuana (37.7%), cocaine and/or crack (40.0%), and whoonga (21.0%). Many participants experienced physical (56.8%) and sexual violence in the past 6 months (41.6%), had at least mild depression symptoms (73.9%), and attempted to commit suicide in the past 6 months (11.1%). Among deceased participants, 30.0% were diagnosed with TB in the past 6 months and 70.0% had CD4 cell count < 200 cells/mm³ at baseline when compared to 13.0% and 18.1% overall, respectively.

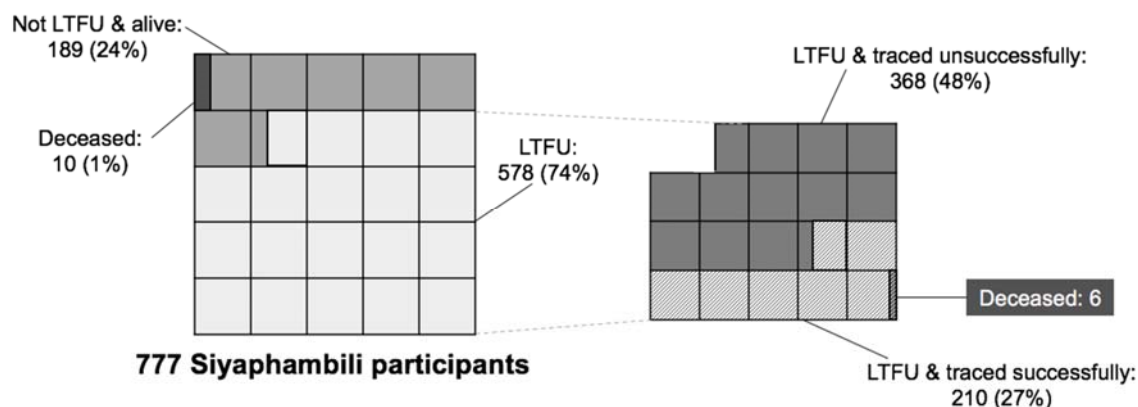


Figure 2. Participant breakdown by vital status, loss to follow-up (LTFU), and tracing status.

Of 578 participants who were initially LTFU for ≥ 6 months, 210 participants later returned for any follow-up visits and had their vital status ascertained (i.e., traced successfully), and were treated as a “tracing sample.”

Table 1. Baseline characteristics of the Siyaphambili participants, 2018-2020 (n=777).

	Dead and not LTFU (N=10)	Alive and not LTFU (N=189)	LTFU (N=578)	Total (N=777)
	n (%)	n (%)	n (%)	n (%)
Age (years)				
18-24	0 (0.0)	22 (11.6)	129 (22.3)	151 (19.4)
25-34	6 (60.0)	117 (61.9)	328 (56.7)	451 (58.0)
35+	4 (40.0)	49 (25.9)	121 (20.9)	174 (22.4)
Missing	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Education				
< Secondary education	9 (90.0)	156 (82.5)	463 (80.1)	628 (80.8)
\geq Secondary education	1 (10.0)	30 (15.9)	114 (19.7)	145 (18.7)
Missing	0 (0.0)	3 (1.6)	1 (0.2)	4 (0.5)
Relationship status				
Single	7 (70.0)	93 (49.2)	301 (52.1)	401 (51.6)
Steady partner living together	1 (10.0)	35 (18.5)	87 (15.1)	123 (15.8)
Steady partner not living together	2 (20.0)	58 (30.7)	190 (32.9)	250 (32.2)
Missing	0 (0.0)	3 (1.6)	0 (0.0)	3 (0.4)
Age at sex work initiation (years)				
≤ 18	1 (10.0)	13 (6.9)	55 (9.5)	69 (8.9)
> 18	9 (90.0)	173 (91.5)	521 (90.1)	703 (90.5)

	Dead and not LTFU (N=10) n (%)	Alive and not LTFU (N=189) n (%)	LTFU (N=578) n (%)	Total (N=777) n (%)
Missing	0 (0.0)	3 (1.6)	2 (0.3)	5 (0.6)
Employment outside sex work				
Sex work only	10 (100.0)	180 (95.2)	548 (94.8)	738 (95.0)
Employment outside of sex work	0 (0.0)	6 (3.2)	29 (5.0)	35 (4.5)
Missing	0 (0.0)	3 (1.6)	1 (0.2)	4 (0.5)
Monthly income (ZAR)				
<=1500	5 (50.0)	67 (35.4)	220 (38.1)	292 (37.6)
1501-3000	3 (30.0)	61 (32.3)	187 (32.4)	251 (32.3)
>3000	2 (20.0)	52 (27.5)	156 (27.0)	210 (27.0)
Missing	0 (0.0)	9 (4.8)	15 (2.6)	24 (3.1)
Number of days selling sex per month				
<20	4 (40.0)	72 (38.1)	207 (35.8)	283 (36.4)
>=20	6 (60.0)	114 (60.3)	366 (63.3)	486 (62.5)
Missing	0 (0.0)	3 (1.6)	5 (0.9)	8 (1.0)
Number of new clients in the past month				
0	0 (0.0)	4 (2.1)	16 (2.8)	20 (2.6)
1-4	1 (10.0)	38 (20.1)	102 (17.6)	141 (18.1)
5-9	4 (40.0)	36 (19.0)	158 (27.3)	198 (25.5)
10-29	3 (30.0)	72 (38.1)	217 (37.5)	292 (37.6)
>=30	2 (20.0)	36 (19.0)	85 (14.7)	123 (15.8)
Missing	0 (0.0)	3 (1.6)	0 (0.0)	3 (0.4)
Number of regular clients in the past month				
0	2 (20.0)	10 (5.3)	25 (4.3)	37 (4.8)
1-4	2 (20.0)	30 (15.9)	106 (18.3)	138 (17.8)
5-9	1 (10.0)	56 (29.6)	148 (25.6)	205 (26.4)
10-29	3 (30.0)	62 (32.8)	215 (37.2)	280 (36.0)
>=30	2 (20.0)	28 (14.8)	84 (14.5)	114 (14.7)
Missing	0 (0.0)	3 (1.6)	0 (0.0)	3 (0.4)
Primary sex work venue				
Indoor	7 (70.0)	137 (72.5)	419 (72.5)	563 (72.5)
Outdoor	3 (30.0)	49 (25.9)	156 (27.0)	208 (26.8)
Missing	0 (0.0)	3 (1.6)	3 (0.5)	6 (0.8)
Housing status				
Not homeless	8 (80.0)	119 (63.0)	364 (63.0)	491 (63.2)
Homeless	2 (20.0)	65 (34.4)	213 (36.9)	280 (36.0)
Missing	0 (0.0)	5 (2.6)	1 (0.2)	6 (0.8)
Travel outside Durban in the past 6 months				
No	10 (100.0)	170 (89.9)	507 (87.7)	687 (88.4)
Yes	0 (0.0)	18 (9.5)	71 (12.3)	89 (11.5)

	Dead and not LTFU (N=10)	Alive and not LTFU (N=189)	LTFU (N=578)	Total (N=777)
	n (%)	n (%)	n (%)	n (%)
Missing	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Heavy alcohol use (5+ drinks 2+ times weekly)				
No	6 (60.0)	102 (54.0)	339 (58.7)	447 (57.5)
Yes	4 (40.0)	84 (44.4)	239 (41.3)	327 (42.1)
Missing	0 (0.0)	3 (1.6)	0 (0.0)	3 (0.4)
Marijuana use in the past 30 days				
No	5 (50.0)	125 (66.1)	350 (60.6)	480 (61.8)
Yes	5 (50.0)	61 (32.3)	227 (39.3)	293 (37.7)
Missing	0 (0.0)	3 (1.6)	1 (0.2)	4 (0.5)
Cocaine and/or crack use in the past 30 days				
No	7 (70.0)	116 (61.4)	342 (59.2)	465 (59.8)
Yes	3 (30.0)	72 (38.1)	236 (40.8)	311 (40.0)
Missing	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Meth, ecstasy, and/or flakk use in the past 30 days				
No	8 (80.0)	178 (94.2)	550 (95.2)	736 (94.7)
Yes	2 (20.0)	10 (5.3)	28 (4.8)	40 (5.1)
Missing	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Heroin use in the past 30 days				
No	10 (100.0)	183 (96.8)	559 (96.7)	752 (96.8)
Yes	0 (0.0)	3 (1.6)	18 (3.1)	21 (2.7)
Missing	0 (0.0)	3 (1.6)	1 (0.2)	4 (0.5)
Whoonga use in the past 30 days				
No	8 (80.0)	152 (80.4)	450 (77.9)	610 (78.5)
Yes	2 (20.0)	34 (18.0)	127 (22.0)	163 (21.0)
Missing	0 (0.0)	3 (1.6)	1 (0.2)	4 (0.5)
Injection drug use in the past 6 months				
No	10 (100.0)	170 (89.9)	551 (95.3)	731 (94.1)
Yes	0 (0.0)	15 (7.9)	25 (4.3)	40 (5.1)
Missing	0 (0.0)	4 (2.1)	2 (0.3)	6 (0.8)
Physical violence in the past 6 months				
No	6 (60.0)	86 (45.5)	240 (41.5)	332 (42.7)
Yes	4 (40.0)	99 (52.4)	338 (58.5)	441 (56.8)
Missing	0 (0.0)	4 (2.1)	0 (0.0)	4 (0.5)
Sexual violence in the past 6 months				
No	7 (70.0)	116 (61.4)	327 (56.6)	450 (57.9)
Yes	3 (30.0)	70 (37.0)	250 (43.3)	323 (41.6)
Missing	0 (0.0)	3 (1.6)	1 (0.2)	4 (0.5)
Depression symptoms				

	Dead and not LTFU (N=10) n (%)	Alive and not LTFU (N=189) n (%)	LTFU (N=578) n (%)	Total (N=777) n (%)
Minimal	2 (20.0)	54 (28.6)	135 (23.4)	191 (24.6)
Mild and above	8 (80.0)	130 (68.8)	436 (75.4)	574 (73.9)
Missing	0 (0.0)	5 (2.6)	7 (1.2)	12 (1.5)
Suicide attempt in the past 6 months				
No	9 (90.0)	168 (88.9)	510 (88.2)	687 (88.4)
Yes	1 (10.0)	17 (9.0)	68 (11.8)	86 (11.1)
Missing	0 (0.0)	4 (2.1)	0 (0.0)	4 (0.5)
Number of health services received in the past 6 months				
<=2	3 (30.0)	88 (46.6)	293 (50.7)	384 (49.4)
>2	7 (70.0)	96 (50.8)	279 (48.3)	382 (49.2)
Missing	0 (0.0)	5 (2.6)	6 (1.0)	11 (1.4)
Hospitalization in the past 6 months				
No	8 (80.0)	160 (84.7)	526 (91.0)	694 (89.3)
Yes	2 (20.0)	26 (13.8)	52 (9.0)	80 (10.3)
Missing	0 (0.0)	3 (1.6)	0 (0.0)	3 (0.4)
TB testing and/or diagnosis in the past 6 months				
Not tested	3 (30.0)	80 (42.3)	239 (41.3)	322 (41.4)
Tested negative	2 (20.0)	83 (43.9)	253 (43.8)	338 (43.5)
Tested positive	3 (30.0)	22 (11.6)	76 (13.1)	101 (13.0)
Tested unknown	2 (20.0)	1 (0.5)	10 (1.7)	13 (1.7)
Missing	0 (0.0)	3 (1.6)	0 (0.0)	3 (0.4)
Duration on ART (years)				
0	0 (0.0)	35 (18.5)	117 (20.2)	152 (19.6)
>0-<1	1 (10.0)	36 (19.0)	112 (19.4)	149 (19.2)
1-<5	4 (40.0)	64 (33.9)	235 (40.7)	303 (39.0)
>=5	5 (50.0)	54 (28.6)	114 (19.7)	173 (22.3)
CD4 cell count (cells/mm3)				
<200	7 (70.0)	30 (15.9)	104 (18.0)	141 (18.1)
200-<500	1 (10.0)	81 (42.9)	251 (43.4)	333 (42.9)
>=500	1 (10.0)	65 (34.4)	195 (33.7)	261 (33.6)
Missing	1 (10.0)	13 (6.9)	28 (4.8)	42 (5.4)
HIV viral load (copies/mL)				
50-1000	2 (20.0)	52 (27.5)	130 (22.5)	184 (23.7)
>1000	8 (80.0)	137 (72.5)	448 (77.5)	593 (76.3)

Loss to follow-up, LTFU; antiretroviral therapy, ART; tuberculosis, TB.

Risk factors of LTFU

In the multivariable model, injection drug use in the past 6 months was associated with reduced LTFU (adjusted HR (aHR): 0.55 , 95% CI: 0.37-0.83); participants experiencing physical violence (aHR: 1.31, 95% CI: 1.08-1.59) and sexual violence in the past 6 months (aHR: 1.39, 95% CI: 1.14-1.70), and having detectable VL (aHR: 1.69, 95% CI: 1.20-2.38, for 50-1000 copies/mL vs. undetectable; aHR: 1.87, 95% CI: 1.37-2.55, for >1000 copies/mL vs. undetectable) were more likely to become LTFU (Table 2). The sensitivity analysis assessing the impact of COVID-19 did not change the findings (results not shown).

Table 2. Characteristics associated with loss to follow-up, 2018-2021 (n=777).

	HR (95% CI)	aHR (95% CI)
Age (years)		
18-24	Ref.	Ref.
25-34	0.71 (0.58-0.87)	0.80 (0.65-0.99)
35+	0.66 (0.51-0.84)	0.90 (0.68-1.18)
Education		
< Secondary education	Ref.	
>= Secondary education	1.13 (0.92-1.39)	
Relationship status*		
Single	Ref.	Ref.
Steady partner living together	0.73 (0.58-0.93)	0.72 (0.57-0.92)
Steady partner not living together	1.03 (0.86-1.24)	1.01 (0.84-1.21)
Age at sex work initiation (years)		
<=18	Ref.	
>18	0.90 (0.68-1.20)	
Employment outside sex work		
Sex work only	Ref.	
Employment outside of sex work	1.02 (0.69-1.49)	
Monthly income (ZAR)		
<=1500	Ref.	
1501-3000	0.97 (0.80-1.18)	
>3000	0.89 (0.73-1.09)	
Number of days selling sex per month*		
<20	Ref.	

	HR (95% CI)	aHR (95% CI)
>=20	1.10 (0.93-1.31)	
Number of new clients in the past month*		
0	Ref.	Ref.
1-4	1.27 (0.85-1.89)	1.12 (0.75-1.69)
5-9	1.40 (0.95-2.07)	1.18 (0.79-1.75)
10-29	1.30 (0.88-1.90)	1.04 (0.71-1.54)
>=30	1.17 (0.77-1.77)	0.90 (0.59-1.39)
Number of regular clients in the past month*		
0	Ref.	
1-4	1.04 (0.71-1.53)	
5-9	1.06 (0.73-1.53)	
10-29	1.17 (0.82-1.68)	
>=30	1.08 (0.73-1.63)	
Primary sex work venue*		
Indoor	Ref.	
Outdoor	1.02 (0.85-1.24)	
Housing status*		
Not homeless	Ref.	
Homeless	1.10 (0.93-1.31)	
Travel outside Durban in the past 6 months*		
No	Ref.	
Yes	1.06 (0.81-1.38)	
Heavy alcohol use (5+ drinks 2+ times weekly)*		
No	Ref.	
Yes	1.05 (0.89-1.25)	
Marijuana use in the past 30 days*		
No	Ref.	Ref.
Yes	1.26 (1.06-1.49)	1.11 (0.93-1.33)
Cocaine and/or crack use in the past 30 days*		
No	Ref.	
Yes	1.07 (0.90-1.26)	
Meth, ecstasy, and/or flakk use in the past 30 days*		
No	Ref.	
Yes	1.12 (0.75-1.67)	
Heroin use in the past 30 days*		
No	Ref.	
Yes	1.29 (0.86-1.94)	
Whoonga use in the past 30 days*		

	HR (95% CI)	aHR (95% CI)
No	Ref.	Ref.
Yes	1.24 (1.02-1.51)	1.23 (0.98-1.55)
Injection drug use in the past 6 months*		
No	Ref.	Ref.
Yes	0.73 (0.51-1.06)	0.55 (0.37-0.83)
Physical violence in the past 6 months*		
No	Ref.	Ref.
Yes	1.63 (1.38-1.93)	1.31 (1.08-1.59)
Sexual violence in the past 6 months*		
No	Ref.	Ref.
Yes	1.78 (1.49-2.11)	1.39 (1.14-1.70)
Depression symptoms*		
Minimal	Ref.	Ref.
Mild and above	1.33 (1.10-1.60)	1.11 (0.91-1.35)
Suicide attempt in the past 6 months*		
No	Ref.	
Yes	1.21 (0.93-1.56)	
Number of health services received in the past 6 months*		
<=2	Ref.	Ref.
>2	0.84 (0.72-1.00)	0.85 (0.71-1.00)
Hospitalization in the past 6 months*		
No	Ref.	
Yes	0.80 (0.60-1.05)	
TB testing and/or diagnosis in the past 6 months*		
Not tested	Ref.	Ref.
Tested negative	1.11 (0.93-1.32)	1.14 (0.95-1.37)
Tested positive	1.32 (1.01-1.72)	1.20 (0.92-1.57)
Tested unknown	0.98 (0.52-1.85)	1.06 (0.55-2.02)
Duration on ART (years)		
0	Ref.	Ref.
>0-<1	0.94 (0.73-1.22)	0.94 (0.72-1.23)
1-<5	0.98 (0.78-1.22)	0.97 (0.77-1.22)
>=5	0.75 (0.58-0.97)	0.80 (0.61-1.06)
CD4 cell count (cells/mm3)		
<200	Ref.	
200-<500	1.03 (0.82-1.30)	
>=500	0.95 (0.74-1.20)	
HIV viral load (copies/mL)*		
<50	Ref.	Ref.

	HR (95% CI)	aHR (95% CI)
50-1000	1.96 (1.40-2.75)	1.69 (1.20-2.38)
>1000	2.31 (1.71-3.11)	1.87 (1.37-2.55)

Note: Values with p-value <0.05 are bolded.

Hazard ratio, HR; adjusted hazard ratio, aHR; confidence interval, CI; antiretroviral therapy, ART; tuberculosis, TB.

*Time-varying variables

Weights used for correction

Among 578 participants who were initially LTFU, 36.3% (210/578) were traced successfully. Of these, 6 (2.9%) additional deaths were identified (Figure 2). In the weighted analysis, the 210 participants who were initially LTFU but traced successfully were assigned the weight of 2.8 (578/210) to stand in for the outcomes of those traced unsuccessfully. The majority of the observed baseline characteristics of the participants who were traced successfully and unsuccessfully were similar (p-value ≥ 0.05), except for whoonga use and CD4 cell count (Table S1). In the past 30 days, 28.1% of LTFU participants who were traced successfully and 18.5% of LTFU participants who were traced unsuccessfully used whoonga (p=0.010); 21.9% of LTFU participants who were traced successfully and 15.8% of LTFU participants who were traced unsuccessfully had CD4 <200 cell/mm³ (p-value=0.011).

Mortality risk

The 18-month unweighted mortality risk was 2.4% (95% CI: 0.8%-3.9%). After weighting, we estimated 18-month mortality risk to be 3.7% (95% CI: 1.8%-5.9%) (Figure 3). Quantitative bias analysis reported 18-month mortality risks ranged from 5.4% (95% CI: 2.4%-9.0%) to 25.3% (95% CI: 10.3%-39.2%) (Figure 4 and Table S2).

The causes of death included TB (n=2), COVID-19 (n=1), cardiomegaly (n=1), hypothermia from homelessness (n=1), violence (n=3), and unknown causes (n=8).

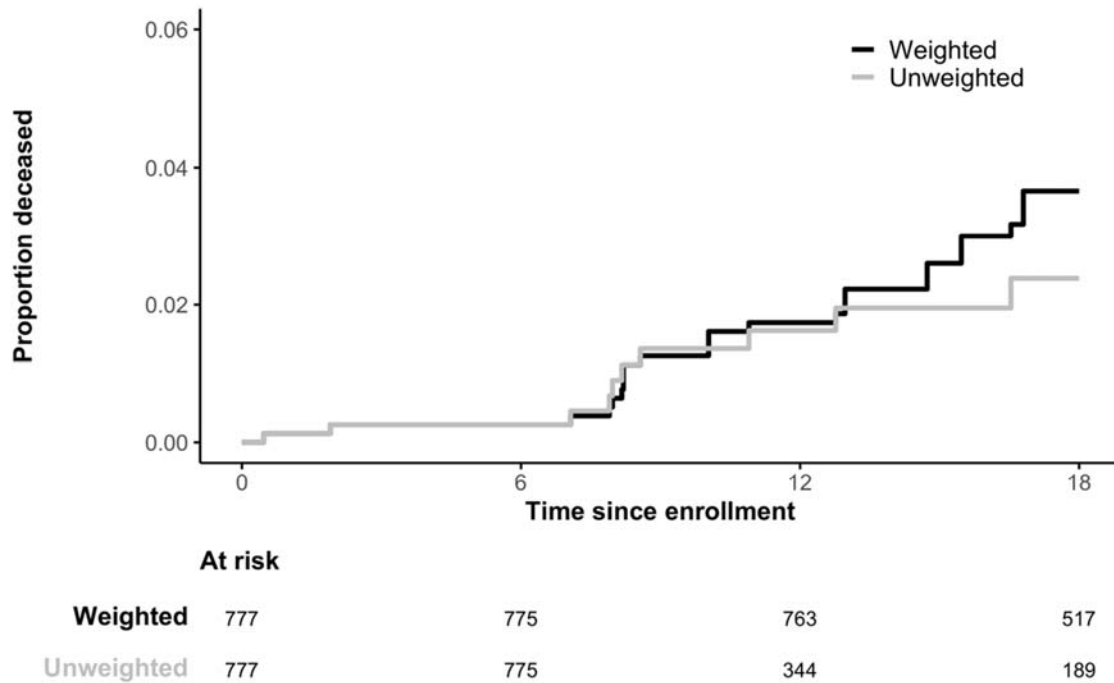


Figure 3. Unweighted and weighted cumulative mortality curves of female sex workers with HIV who enrolled into the Siyaphambili trial, which evaluated strategies for improved viral suppression in Durban, South Africa, 2018-2021. The weighted analysis upweighted the outcomes of the participants in the “tracing sample” who were initially lost to follow-up for ≥ 6 months but later had their vital status ascertained, to stand in for the outcomes of FSW who were lost to follow-up and did not return.

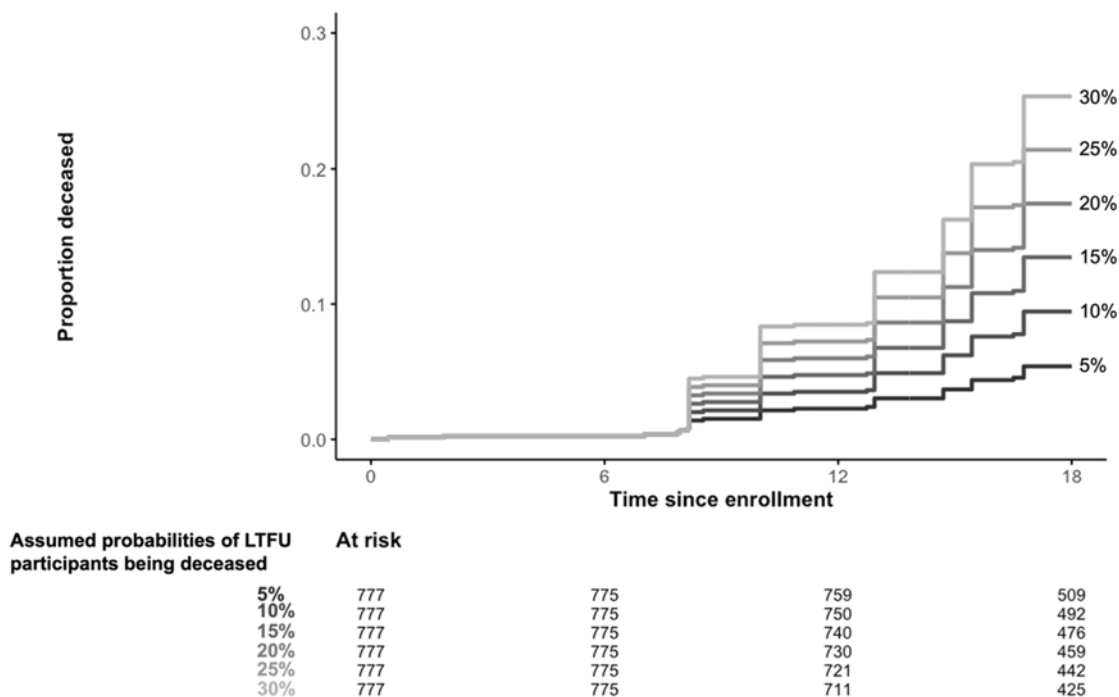


Figure 4. Weighted cumulative mortality curves of female sex workers with HIV who enrolled into the Siyaphambili trial, which evaluated strategies for improved viral suppression in Durban, South Africa, 2018-2021, from the quantitative bias analysis, which allowed the outcomes of the LTFU participants who were traced successfully to stand in for the outcomes of those who we could not trace using the tracing weight and assumed 5-30% of the LTFU participants being deceased within 18 months.

Discussion

Since high LTFU challenges outcome assessment, we attempted to correct the under-ascertained mortality among FSW with an unsuppressed HIV VL in Durban, South Africa. Three-quarters of FSW enrolled into this study that evaluated strategies for improved viral suppression were LTFU for at least 6 months within the 18-month study. When correcting for LTFU using inverse probability of tracing weights, the cumulative weighted mortality risk within 18-months was 3.7%, almost twice as much as the unweighted

estimate. The leading causes of death that we could ascertain were TB and violence, which corresponded to the risk factors of LTFU, non-viral suppression and violence. This suggests how LTFU participants could have an increased hazard of death. Accurately estimating the mortality risk of FSW requires addressing LTFU.

Despite finding a higher number of LTFU than those reported in existing literature (9,13,14,45), few risk factors of LTFU were identified, which suggests consistently high vulnerabilities experienced by all FSW. This supposition is supported by high proportions of participants reporting experiencing homelessness, heavy alcohol use, illicit drug use, depression, and suicidal ideation. Sustained non-viral suppression was a risk factor of LTFU despite having conducted formative research to enhance the fit of the Siyaphambili interventions to facilitate viral suppression (23). Non-viral suppression, particularly among those with low CD4 cell count, can increase the risk of opportunistic infections, including TB, and mortality (46). Moreover, the participants who experienced physical and sexual violence were more likely to become LTFU. FSW who experienced violence might hesitate to seek help or avoid accessing health services due to fear of arrest (47) or prior mistreatment in healthcare setting (47,48), increasing their risks of disengagement from care and death. Future research should explore other integrated interventions that address psychosocial barriers, including those related to violence, and provide TB screening, treatment, and prevention to avoid preventable deaths.

Our weighted 18-month mortality risk of FSW has increased but is likely underestimated. When compared to the mortality estimates reported among general PWH (16,28,30–34,37), our magnitude is smaller despite that FSW were non-virally suppressed and experienced psychosocial vulnerabilities. When compared to previous tracing studies conducted among general PWH in South Africa (19,20), our reported 2.9% probability of

death in the tracing sample was much lower likely due to our tracing sample being limited to the existing trial data of individuals who experienced interrupted care. A study from Uganda found FSW with phones were less likely to be LTFU than those without (9), and phone ownership in this study was highly dynamic (49), which might limit our tracing success (50). Other tracing approaches conducted in South Africa have linked participants' identity to the vital registration system, which has a high level of completeness (18,36,37). We could not use this approach because we did not collect participants' national identification to preserve the participants' privacy and as many sex workers do not have or lose their identification. Further, the FSW were highly mobile and/or might have silently transferred care elsewhere (44,51,52). From the quantitative bias analysis, we speculate the 18-month mortality risk to be closer to 5.4% assuming 5% of LTFU participants had died given the expanded ART access, increase in silent transfers, and fallen mortality risk in the past decades (20,37,53,54). The mortality risk might be closer to 25.3% if we assumed LTFU FSW with non-viral suppression had a much higher risk of death compared to the general PWH in the Treat-All era. Further study is needed and requires a more targeted and tailored approach to trace marginalized and mobile populations.

There are important limitations in this study. Firstly, the interpretation of risk factors of LTFU must be carefully considered as LTFU has several meanings (16–18). Future studies should differentiate silent transfer from disengagement from care. Secondly, our weighted analysis assumed that LTFU participants who were traced successfully and traced unsuccessfully were exchangeable despite the difference in observed whoonga use and CD4 cell count. Unobserved variables and vital status might be associated with LTFU. Future studies should trace a random sample of LTFU participants to correct the mortality estimate (28,32,55). Thirdly, our study followed the participants for up to 18 months after they had

an unsuppressed HIV VL test and enrolled in an intervention trial. Our findings have practical implications for program implementation, but future studies should explore different time origins, such as HIV diagnosis and ART initiation, which may be more clinically meaningful for overall FSW with HIV. Lastly, while we conducted our study among FSW with an unsuppressed HIV VL in Durban, South Africa, the interpretation of under-ascertained mortality may be generalizable to the broader FSW with HIV in similar settings given the dynamic state of vulnerability, although the magnitude of the estimate may differ (56).

Conclusions

The mortality risk of FSW with HIV in Durban, South Africa, who experienced heightened burden of violence, homelessness, alcohol and substance use, depression, and suicide ideation, would be underestimated if not accounting for the increased hazard of death due to LTFU. Programs aiming to support the health and wellbeing of FSW must address psychosocial risks to optimize engagement in care and prevent unnecessary deaths.

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HH, CC, MM, DP, VG, SM, SB, and SS designed and implemented the study. CC, MM, LS, SM, and VG led data collection. SL conducted data analysis and wrote the first draft of the manuscript under the supervision of CC, SB, and SS. All authors reviewed the manuscript and provided feedback.

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Supplementary Materials

Figure S1. Swimmer plots illustrating the 18-month timeline of vital status ascertainment and loss to follow-up (LTFU) classification for hypothetical participants in Siyaphambili study. The solid circle represents death occurrence.

Table S1. Observed baseline characteristics of loss to follow-up participants who were traced successfully and traced unsuccessfully (n=578).

Table S2. The weights used in the quantitative bias analysis and the weighted 18-month mortality risks of female sex workers with HIV who enrolled into the Siyaphambili trial, which evaluated strategies for improved viral suppression in Durban, South Africa, 2018-2021, allowing the outcomes of the LTFU participants who were traced successfully to stand in for the outcomes of those who we could not trace using the tracing weight and assuming 5-30% of the LTFU participants being deceased within 18 months.