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Longitudinal Patterns and Predictors of Opioid and Stimulant Use Initiation and Cessation among Female Sex Workers Living with HIV in South Africa

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Abstract

Female sex workers (FSW) are disproportionately impacted by HIV and substance use. Substance use has been linked to poor HIV treatment outcomes, necessitating exploration of substance use patterns — including polysubstance use — and predictors among FSW living with HIV.

Data were obtained for 777 FSW living with HIV who were not virally suppressed and previously randomized to *Siyaphambili*, a trial of HIV treatment support strategies implemented through TB HIV Care in eThekwini, South Africa. FSW were asked about recent marijuana, opioid, stimulant, and hazardous alcohol use at enrollment and semi-annually for 18 months from June 2018-January 2022. We estimated incidence of substance use initiation/cessation post-enrollment and used Kaplan-Meier plots and lasagna plots to visualize trends. Cox proportional hazards models assessed baseline predictors of substance use initiation/cessation.

Overall, 454 FSW (58.4%) reported any opioid and/or stimulant use. Prior visit hazardous alcohol use (aHR: 0.20, 95% CI 0.09-0.41) and prior-visit stimulant use (aHR: 2.80, 95% CI 1.23-6.37) were negatively and positively associated with opioid initiation, respectively. Prior visit marijuana use (aHR: 1.75, 95% CI 1.11-2.75) and opioid use (aHR: 5.31, 95% CI 3.32-8.51) were positively associated with stimulant initiation.

We found a high prevalence of substance use among FSW living with HIV that was dynamic over time, including a shared relationship between opioid and stimulant use that suggests intertwined substance use. Further investigation into the impact of polysubstance use patterns on success of HIV support strategies is needed to inform HIV treatment and harm reduction programming.

Keywords: HIV care, HIV treatment, substance use, sub-Saharan Africa

1. Introduction

Female sex workers (FSW) in sub-Saharan Africa and their clients are disproportionately impacted by HIV, and their unmet treatment needs contribute to both individual HIV morbidity and mortality and population-level HIV outcomes. Recent estimates show that the unmet HIV prevention and treatment needs among FSW account for 15% of incident HIV infections in the region (Stevens et al., 2024). Moreover, HIV appears more prevalent among FSW in South Africa than among FSW in other eastern and southern African nations (Stevens et al., 2024), with a population prevalence approximating 60% (Milovanovic et al. 2021). Prior studies have found that retention in HIV care is suboptimal among FSW living with HIV in South Africa (Schwartz et al., 2017) and other southern African nations (Boothe et al., 2021; Lancaster et al., 2016; Rucinski et al., 2020). An estimated 74% of FSW living with HIV in South Africa who are on anti-retroviral therapy (ART) are virally suppressed (Jaffer et al., 2022); in eThekwini, only 38% of FSW living with HIV are virally suppressed (Rosen et al., 2024).

Illicit drug use has been identified as a barrier to retention in HIV care (Degarege et al., 2022; Parmley et al., 2020; Wechsberg et al., 2017) and a predictor of suboptimal HIV outcomes (Baum et al., 2009) in many populations, including FSW (Parmley et al., 2020). Anticipated and enacted substance use stigma from HIV care providers (Mlunde et al., 2024; Regenauer et al., 2020) and missing ART doses while under the influence of illicit drugs (Parmley et al., 2020; Yang et al., 2017) are commonly reported barriers to ART uptake or adherence among people living with HIV in sub-Saharan Africa. Prior studies have demonstrated that polysubstance use is common among FSW in South Africa (Parry et al., 2008; Rosen et al., 2024; Yeo et al., 2022) and other sub-Saharan African countries (Beksinska et al., 2022; Nelson, 2013; Syvertsen et al., 2019), with FSW often using stimulants to help them meet the physical demands of sex work over long hours (Needle et al., 2008; Nelson, 2013; Parry et al., 2008) and using alcohol, marijuana, and/or opioids to relax (Mbonye et al., 2014; Needle et al., 2008; Nelson, 2013) and cope with the emotional toll, discomfort, and occupational hazards of sex work (e.g., condom coercion, client- and officer-perpetrated violence) (Mbonye et al., 2014; Nelson, 2013; Syvertsen et al., 2019). Cross-sectional studies have found that South African FSW engaging in polysubstance use are significantly more likely to report homelessness, outdoor sex work, and HIV-related and intersectional stigma, as well as experiences of physical and sexual violence (Jewkes et al., 2021; Rosen et al., 2024; Yeo et al., 2022).

Changes in polysubstance use over time may also have important implications for HIV treatment success and other health outcomes among FSW in South Africa. Longitudinal studies characterizing patterns of substance use in high-income settings have found that periods of opioid and stimulant use are associated with ART non-adherence and viral rebound (Azar et al., 2015; Jones et al., 2022; Ladak et al., 2019). However, data documenting changes in polysubstance use over time among FSW in low- and middle-income countries are limited, as are data assessing predictors of these changes and their impact on HIV service delivery. Further, there has been no longitudinal study of patterns and predictors of substance use initiation and cessation with FSW in South Africa. Thus, the goal of this analysis is to characterize temporal

patterns of opioid and stimulant use among FSW living with HIV in South Africa and identify predictors of changing substance use patterns over time.

2. Materials and methods

2.1. Study population

Data for these analyses were derived from *Siyaphambili*, a sequential multiple assignment randomized trial (SMART) evaluating the comparative effectiveness and efficiency of two HIV treatment strategies among virally unsuppressed female sex workers (FSW) living with HIV in eThekwini, South Africa. The methods underlying this trial have been previously described (Comins et al., 2019). Briefly, *Siyaphambili* was implemented by TB HIV Care, a South African non-profit organization and leading provider of HIV prevention and treatment services to FSW nationally. Cisgender FSW aged ≥ 18 years, aware of their HIV status for at least 6 months, living in eThekwini, speaking English or isiZulu, and not pregnant at the time of enrollment were eligible to participate in the trial. At enrollment, FSW exhibiting unsuppressed viral loads (> 50 HIV RNA copies/ml) were randomized to either a mobile van-based decentralized treatment program (DTP) or a peer-led individualized case management (ICM) intervention for 6 months. At the 6-month follow-up visit, FSW achieving viral suppression were re-randomized back to the programmatic standard of care (HIV treatment free of charge at the drop-in center and community outreach through peer educators and mobile family planning, STI treatment and condom/lube provision) or to continue their previously assigned intervention for the remainder of the study. FSW who remained virally unsuppressed were re-randomized to either continue their previously assigned intervention or to receive a combination of the two interventions (DTP + ICM) for the remainder of the study. Only data for the FSW who were randomized into the trial and re-randomized at 6 months (n = 777) were included in the analysis; individuals who were virally suppressed at baseline were not eligible for randomization and, thus, were excluded from the trial.

2.2. Data collection

HIV treatment strategies tested as part of *Siyaphambili* were implemented through research team members employed by TB HIV Care. Although the DTP and ICM strategies were implemented regularly (at least quarterly), intervention delivery occurred separately from semi-annual study visits, which were conducted at enrollment and at 6, 12, and 18 months. During the semi-annual visit, study team members administered a structured quantitative questionnaire to study participants and assessed viral load through blood samples sent to the National Health Laboratory System. FSW were enrolled in *Siyaphambili* from June 2018-March 2020, and data collection concluded in January 2022. Attempts — comprising phone calls, text messages, and physical tracing — were made to complete study visits and follow up on outcomes through trial endline.

The questionnaire administered at each study visit assessed various aspects of health, HIV risk behavior, and quality of life, including modules on sexual history and reproductive health, physical and sexual health, substance use, social support, and stigma.

2.3 Substance use outcomes

Substance use, the primary outcome explored through these analyses, was assessed via self-reported use in the last 30 days of the following drugs: marijuana, cocaine, whoonga (a combination drug typically smoked and consisting of heroin, marijuana, and efavirenz, a non-nucleoside reverse transcriptase inhibitor found in ART regimens) (Grelotti et al., 2014), ecstasy, methamphetamine, heroin, crack, flakka/cat (synthetic form of the flowering plant khat that contains the active ingredients cathine and cathinone) (Patocka et al., 2020), and other unenumerated drugs in the last 30 days. Participants were also asked how often they had a drink containing alcohol, how many standard drinks containing alcohol they had during a typical day when they were drinking, and how often they had 6 or more drinks on one occasion — the 3 items comprising the Alcohol Use Disorders Identification Test C (AUDIT-C) (Bush et al., 1998) — to assess the prevalence and frequency of alcohol use in the study population.

Substance use variables were collapsed into dichotomous variables assessing any hazardous alcohol use, any opioid use, and any stimulant use at each timepoint. The "hazardous alcohol use" variable captured FSW who received a score of 3 or higher on the AUDIT-C at each timepoint, in accordance with AUDIT-C scoring guidelines for females (Bush et al., 1998). An error in the coding of the baseline questionnaire resulted in errant omission of binge drinking assessment in initial questionnaires and a missing outcome for n = 18; multiple imputation by chained equations (MICE) (Azur et al., 2011) was used to impute the dichotomous hazardous alcohol use variable for these individuals. Enrollment date, age, education status, housing status, log-transformed monthly income, relationship status, parity, % of income that comes from sex work, sex work venue type, sex work-related arrest history, receipt of physical and sexual violence, depression, recent suicide attempt, social support, HIV- and sex work-related stigma, internalized stigma, and baseline marijuana, opioid, and stimulant use were used to probabilistically determine baseline hazardous alcohol use status for these FSW. At each timepoint, the opioid use and stimulant use variables captured FSW who reported using any opioids (i.e., heroin, whoonga) and stimulants (i.e., cocaine, crack, methamphetamine, ecstasy, flakka/cat), respectively, at each study visit. Marijuana use was treated as its own drug use class across analyses.

2.4. Analysis

All analyses were conducted in RStudio version 4.2.3.

2.4.1. Individual substance use trajectories

First, lasagna plots were generated to visualize individual opioid and stimulant use trajectories over study visits (Swihart et al., 2010). Substance use trajectories for individuals who completed

two or more study visits were descriptively characterized and are presented in supplemental tables (n = 570, Table S1).

2.4.2. Time-to-event analyses

Time-to-event analyses were used to assess patterns of substance use initiation and cessation. Initiation was defined as incident opioid or stimulant use, respectively, after first visit, while cessation was defined as discontinuation of opioid or stimulant use, respectively, after first visit. Only individuals who provided information on their substance use during two or more study visits were included in these analyses (n = 570). However, output from Fisher's exact tests comparing rates of substance use at baseline between FSW who completed two or more study visits and FSW who only completed one study visit are presented in supplemental tables (Table S2). Initiation analyses were restricted to individuals who did not report use of a specified substance at baseline; likewise, cessation analyses were restricted to individuals who reported baseline use of the substance. Kaplan-Meier survival estimates using calendar time as the time metric were obtained for initiation and cessation of opioid and stimulant use. Univariable and multivariable Cox proportional hazards models assessed whether use of other substances (hazardous alcohol, marijuana, and opioid/stimulant use) at the prior study visit (time-varying, lagged exposure) and other relevant baseline covariates were predictors of opioid and stimulant initiation or cessation, respectively. Output from univariable models assessing baseline use of other substances (time-fixed) and concurrent use of other substances (time-varying) as predictors of opioid and stimulant initiation and cessation are presented alongside results from the lagged substance use models in the supplement to compare alternative approaches to including substance use as a predictor (Table S3).

Other covariates assessed in these models included age at study enrollment (< 30 vs. ≥ 30 years); education status (secondary education complete vs. incomplete); recent homelessness (yes/no, described living arrangement in the last 6 months as "no place to live/homeless"); past-month income (log-transformed in South African Rand [ZAR]); relationship status (currently has a steady partner vs. no steady partner); parity (ever vs. never had a live birth); percentage of past-month income earned from sex work (treated continuously); primary sex work venue type (indoor vs. outdoor primary venue, where FSW who primarily had sex with clients in the street/park/public garden, on the beach, or in a private vehicle were considered FSW with outdoor primary venues); arrest history (ever vs. never arrested on prostitution charges); lifetime physical violence receipt (ever vs. never pushed, shoved, slapped, hit, kicked, choked, or otherwise physically hurt) and sexual violence receipt (ever vs. never sexually assaulted/raped), both adapted from the WHO Violence Against Women Instrument (Schraiber et al., 2010); severity of depression symptoms, as assessed by the Patient Health Questionnaire-9 (PHQ-9) (low-to-mild vs. moderate-to-severe depression in the last 2 weeks) (Kroenke and Spitzer, 2002); recent suicide attempt (yes/no in the 6 months preceding enrollment); social support, as measured by the Medical Outcomes Study Social Support Scale (MOS:SSS) (low, moderate, or high social support) (Drain et al., 2015); and HIV-related, sex work-related, and internalized stigma, as measured by a stigma scale that has been used and validated in other populations of FSW with HIV (ever experienced any stigma, yes/no) (Grosso et al., 2019; Lyons et al., 2020).

Since the MOS:SSS and stigma scales used in this study do not have validated cutpoints for categorical classifications, we defined "low social support" as scores ≤8, "moderate social support" as scores between 9 and 16, and "high social support" as scores > 16 on the MOS:SSS. Furthermore, we defined "any HIV-related stigma" and "any sex work-related stigma" as answering "yes" to any of the items assessing these constructs, and "any internalized stigma" as answering "strongly disagree" or "disagree" to any of the 3 reverse-coded Likert scale items assessing this construct.

The associations between each of the described covariates and opioid and stimulant use initiation and cessation, respectively, were assessed using univariable and multivariable Cox proportional hazards models. Covariates that were associated with opioid or stimulant initiation or cessation, respectively, at the $p < 0.1$ level in univariable models were included in multivariable models and used to estimate adjusted hazard ratios (aHRs) with 95% confidence intervals (CI). A global test of proportional hazards was performed on each multivariable model to examine whether the proportional hazards assumption was upheld. Calendar time with late entries was used as the time metric for all time-to-event analyses to account for secular trends in substance use initiation and cessation across the study population. Individuals who did not provide information about their opioid or stimulant use at enrollment but did provide this information at subsequent study visits entered the analysis at the visit during which they first provided this information.

3. Results

3.1. Descriptive statistics

Baseline questionnaires were available for 775/777 FSW randomized to the HIV treatment support interventions in *Siyaphambili*. The 6-month follow-up questionnaire was completed by 385 FSW (49.5% of those enrolled), while 396 (51.0%) completed the 12-month follow-up questionnaire, and 444 (57.1%) completed the 18-month follow-up questionnaire. Overall, 570 women (73.4%) completed two or more visits. Characteristics of the study population at enrollment are presented in Table 1.

All 775 women who completed a baseline questionnaire provided some information on their past-month substance use. At baseline, 524 FSW (67.6%) exhibited symptomology of hazardous alcohol use, 292 (37.7%) reported any past-month marijuana use, 168 (21.7%) reported any past-month opioid use, and 344 (44.4%) reported any past-month stimulant use. Over half (55.1%) of FSW reported baseline polysubstance use, defined as past-month use of 2 or more of these substance types. Only 44 FSW reported ever injecting drugs at baseline (5.7%), with 40 of those FSW reporting having injected drugs in the last 6 months (5.2%). Prevalence of use of specific substances at enrollment is provided in Table 1.

Table 1: Characteristics of FSW in the *Siyaphambili* trial at baseline visit (n = 775). The baseline *Siyaphambili* questionnaire assessed demographic information, sex work conditions, experiences with physical and sexual violence, mental health, social

support, stigma, and substance use and was completed by 775 FSW. The number of FSW who endorsed or screened positively for each characteristic are presented as a proportion of the total number of FSW who answered each question (excluding those who chose not to answer from the denominator).

Characteristic	Count (% of total enrolled) / Median (IQR)
Demographics	
Median age, years (IQR)*	29 (25-34)
Age ≥ 30 years	361/773 (46.7)
Secondary education complete	145/773 (18.8)
Recently homeless (≤6 months)	77/771 (10.0)
Median monthly income, ZAR (IQR)*	2000 (1000-3400)
Currently has steady partner	371/774 (47.9)
Ever given birth	599/772 (77.6)
Sex work	
Median % of income that comes from sex work (IQR)*	100 (80-100)
Outdoor primary sex work venue	205/771 (26.6)
Ever arrested on prostitution charges	309/773 (39.9)
Receipt of physical and sexual violence	
Ever experienced physical violence	446/774 (57.6)
Ever experienced sexual violence through rape	325/773 (42.0)
Mental health and social support	
Low-to-mild depression (past 2 weeks)[a]	513/773 (66.4)
Moderate-to-severe depression (past 2 weeks)	260/773 (33.6)
Recent suicide attempt (≤6 months)	86/705 (12.2)
Low social support[b]	121/773 (15.7)
Moderate social support	185/773 (23.9)
High social support	467/773 (60.4)
Stigma (ever vs. never)	
No HIV-related stigma	448/773 (58.0)
Any HIV-related stigma[c]	325/773 (42.0)
No sex work-related stigma	180/773 (23.3)
Any sex work-related stigma[c]	593/773 (76.7)
No internalized stigma	334/773 (43.2)
Any internalized stigma[d]	439/773 (56.8)
Substance use (≤6 months)	
Any alcohol use	531/773 (68.6)
Marijuana use	292/775 (37.7)
Cocaine use	87/775 (11.2)
Ecstasy use	33/775 (4.3)
Methamphetamine use	12/775 (1.5)

Crack use	270/775 (34.8)
Flakka/cat use	2/775 (0.3)
Whoonga use	162/775 (20.9)
Heroin use	21/775 (2.7)
Ever injected drugs	44/772 (5.7)
Injected drugs recently (≤6 months)	40/772 (5.2)

*Age, monthly income, and sex work income data were available for 773, 768, and 767 FSW, respectively
[a]Low-to-mild depression defined as PHQ-9 scores from 0-10, moderate-to-severe depression defined as PHQ-9 scores >10
[b]Low social support defined as MOS:SSS score from 0-8, moderate social support defined as scores from 9-16, high social support defined as scores >16
[c]Any HIV- or sex work-related stigma defined as answering "yes" to any question assessing HIV- and sex work-related stigma
[d]Any internalized stigma defined as answering "disagree" or "strongly disagree" to reverse-coded questions assessing internalized stigma

3.2. Individual substance use trajectories

Lasagna plots depict individual opioid and stimulant use trajectories over follow-up for all 777 *Siyaphambili* participants who were randomized to an HIV treatment support intervention after enrollment visit (Figure 1). Lasagna plots depicting individual opioid and stimulant use trajectories stratified by use of other substances at first visit are presented in Figure S1. These plots reveal a high overall prevalence of stimulant use in the *Siyaphambili* cohort relative to opioid use, as well as greater consistency in opioid use relative to stimulant use across study visits.

3.3. Time-to-event analyses

During follow-up, 35/446 (7.8%) of FSW not reporting opioid use at baseline initiated opioids, and 75/307 (24.4%) of FSW not reporting stimulant use at baseline initiated stimulants. Similarly, 41/124 (33.1%) FSW reporting opioid use at baseline discontinued opioid use, and 137/263 (52.1%) FSW reporting stimulant use at baseline discontinued stimulant use during follow-up. Kaplan-Meier curves depict overall first study follow-up initiation and cessation of opioid and stimulant use, respectively, during the study period, with calendar time as the time metric (Figure 2a, b).

3.3.1. Correlates of initiation

Multivariable Cox proportional hazards models revealed that opioid initiation was inversely associated with hazardous alcohol use reported at the prior study visit (aHR=0.20, 95% CI: 0.09-0.41), but positively associated with stimulant use at the prior study visit (aHR=2.80, 95% CI: 1.23-6.37). Ever being arrested on sex work-related charges (aHR=1.63, 95% CI: 1.05-2.52), marijuana use at the prior study visit (aHR=1.75, 95% CI: 1.11-2.75), and opioid use at the prior study visit (aHR=5.31, 95% CI: 3.32-8.51) were positively associated with stimulant initiation. All results from unadjusted and adjusted Cox proportional hazards models assessing predictors of opioid and stimulant initiation are presented in Table 2.

Global tests of proportional hazards showed no evidence that the proportional hazards assumption was violated in any multivariable model except the model for stimulant initiation (p = 0.0011). Tests of proportional hazards for individual covariates in this model revealed non-proportional hazards of stimulant initiation over follow-up among FSW aged ≥ 30 (p = 0.0411), engaged in prior-visit hazardous alcohol use (p = 0.0389), or engaged in prior-visit opioid use (p < 0.0001). Notably, the relative hazard of stimulant initiation appeared to increase steadily over time and then decrease toward the end of follow-up among FSW engaged in prior-visit opioid use. Despite these violations, this model was maintained in the analysis; recent literature suggests that hazard ratios can be interpreted as weighted averages of the time-varying hazard in circumstances where the proportional hazards assumption is violated, which commonly occurs in medical studies (Stensrud and Hernán, 2020).

3.3.2. Correlates of cessation

Being aged ≥ 30 years at enrollment (aHR=3.43, 95% CI: 1.77-6.68) and having experienced any HIV-related stigma (aHR=2.06, 95% CI: 1.09-3.91) were positively associated with opioid cessation, while having any internalized stigma was inversely associated with opioid cessation (aHR=0.40, 95% CI: 0.19-0.83). Having high social support (aHR=2.00, 95% CI: 1.22-3.29) was the only significant predictor of stimulant cessation. All results from unadjusted and adjusted Cox proportional hazards models assessing predictors of opioid and stimulant cessation are presented in Table 3. Global tests of proportional hazards showed no evidence that the proportional hazards assumption was violated.

Table 2: Predictors of opioid and stimulant initiation among FSW in the *Siyaphambili* cohort who provided information on recent substance use at two or more study visits (n = 570). All covariates are time-fixed at baseline except substance use covariates, which were lagged to the prior visit at each timepoint.

	Opioid Initiation (n=XX)		Stimulant Initiation (n=XX)	
Predictor	**HR (95% CI)**	**Adjusted HR (95% CI)**	**HR (95% CI)**	**Adjusted HR (95% CI)**
Demographics				
Age ≥ 30	0.49 (0.24, 0.98)*	0.99 (0.42, 2.31)	0.60 (0.38, 0.94)*	0.76 (0.49, 1.18)
Secondary education complete	0.49 (0.17, 1.38)		0.69 (0.35, 1.34)	
Recently homeless	2.19 (0.70, 6.83)		1.74 (0.79, 3.84)	
Log-transformed monthly income (ZAR)	0.95 (0.72, 1.26)		1.11 (0.86, 1.45)	
Currently has steady partner	1.41 (0.72, 2.77)		1.01 (0.65, 1.58)	
Ever given birth	0.32 (0.17, 0.63)***	0.55 (0.24, 1.30)	1.08 (0.59, 1.98)	
Sex work				
Proportion of income that comes from sex work	0.27 (0.08, 0.97)*	0.37 (0.10, 1.34)	3.69 (0.83, 16.39)	2.77 (0.71, 10.87)
Outdoor primary sex work venue	1.43 (0.67, 3.04)		1.52 (0.94, 2.45)	1.25 (0.76, 2.06)

Ever arrested on prostitution charges	1.94 (0.97, 3.88)	1.52 (0.74, 3.11)	1.63 (1.03, 2.58)*	1.63 (1.05, 2.52)*
Receipt of physical and sexual violence				
Ever experienced physical violence	0.53 (0.27, 1.05)	0.55 (0.27, 1.12)	1.10 (0.70, 1.73)	
Ever raped	0.75 (0.36, 1.56)		1.43 (0.90, 2.26)	
Mental health and social support				
Low-to-mild depression	REF		REF	
Moderate-to-severe depression	1.11 (0.56, 2.21)		0.98 (0.61, 1.58)	
Recent suicide attempt	1.54 (0.60, 3.97)		1.38 (0.69, 2.75)	
Low social support	REF		REF	
Moderate social support	0.63 (0.18, 2.20)		0.92 (0.42, 1.99)	
High social support	1.42 (0.50, 3.99)		1.18 (0.57, 2.43)	
Stigma				
No HIV-related stigma	REF		REF	
Any HIV-related stigma	1.35 (0.68, 2.67)		0.88 (0.55, 1.41)	
No sex work-related stigma	REF		REF	
Any sex work-related stigma	1.91 (0.74, 4.94)		1.25 (0.76, 2.06)	
No internalized stigma	REF		REF	
Any internalized stigma	1.57 (0.77, 3.22)		1.20 (0.76, 1.90)	
Substance use lagged to prior visit				
Hazardous alcohol use at prior visit	0.16 (0.08, 0.32)***	0.20 (0.09, 0.41)***	0.55 (0.36, 0.86)**	1.11 (0.70, 1.76)
Marijuana use at prior visit	3.09 (1.56, 6.09)**	2.07 (0.90, 4.72)	2.35 (1.50, 3.70)***	1.75 (1.11, 2.75)*
Opioid use at prior visit	NA		6.07 (3.92, 9.42)***	5.31 (3.32, 8.51)***
Stimulant use at prior visit	3.27 (1.62, 6.59)***	2.80 (1.23, 6.37)*	NA	
***p < 0.05; **p < 0.01; ***p < 0.001**				

Table 3: Predictors of opioid and stimulant cessation among FSW in the *Siyaphambili* cohort who provided information on recent substance use at two or more study visits (n = 570). All covariates are time-fixed at baseline except substance use covariates, which were lagged to the prior visit at each timepoint.

	Opioid Cessation (n=XX)		**Stimulant Cessation (n=XX)**	
Predictor	**HR (95% CI)**	**Adjusted HR (95% CI)**	**HR (95% CI)**	**Adjusted HR (95% CI)**
Demographics				
Age ≥ 30	3.43 (1.86, 6.33)***	3.43 (1.77, 6.68)***	1.40 (1.01, 1.96)*	1.36 (0.97, 1.9)
Secondary education complete	1.36 (0.68, 2.70)		0.98 (0.69, 1.41)	
Recently homeless	0.62 (0.30, 1.28)		0.73 (0.42, 1.28)	
Log-transformed monthly income (ZAR)	1.17 (0.88, 1.55)		1.08 (0.93, 1.26)	
Currently has steady partner	0.93 (0.51, 1.70)		1.23 (0.89, 1.69)	

Ever given birth	1.67 (0.86, 3.25)		1.30 (0.91, 1.85)	
Sex work				
Proportion of income that comes from sex work	0.91 (0.71, 1.16)		1.04 (0.84, 1.30)	
Outdoor primary sex work venue	0.95 (0.52, 1.75)		0.74 (0.49, 1.12)	
Ever arrested on prostitution charges	1.49 (0.83, 2.69)		1.35 (0.98, 1.86)	1.28 (0.91, 1.81)
Receipt of physical and sexual violence				
Ever experienced physical violence	1.21 (0.60, 2.42)		1.00 (0.71, 1.41)	
Ever raped	0.98 (0.54, 1.79)		0.79 (0.57, 1.09)	
Mental health and social support				
Low-to-mild depression	REF		REF	
Moderate-to-severe depression	1.23 (0.65, 2.32)		1.01 (0.72, 1.40)	
Recent suicide attempt	2.16 (1.01, 4.62)*	1.89 (0.95, 3.78)	1.13 (0.64, 2.02)	
Low social support	REF		REF	
Moderate social support	0.91 (0.37, 2.24)		1.24 (0.73, 2.13)	1.49 (0.85, 2.64)
High social support	1.41 (0.64, 3.09)		1.90 (1.19, 3.02)**	2.00 (1.22, 3.29)**
Stigma				
No HIV-related stigma	REF		REF	
Any HIV-related stigma	2.39 (1.32, 4.32)**	2.06 (1.09, 3.91)*	1.41 (1.01, 1.97)*	1.32 (0.93, 1.87)
No sex work-related stigma	REF		REF	
Any sex work-related stigma	1.05 (0.53, 2.08)		1.10 (0.73, 1.67)	
No internalized stigma	REF		REF	
Any internalized stigma	0.58 (0.31, 1.05)	0.40 (0.19, 0.83)*	0.75 (0.54, 1.04)	0.73 (0.53, 1.02)
Substance use lagged to prior visit				
Hazardous alcohol use at prior visit	0.91 (0.47, 1.73)		1.18 (0.86, 1.62)	
Marijuana use at prior visit	1.32 (0.75, 2.31)		0.83 (0.62, 1.13)	
Opioid use at prior visit	NA		0.76 (0.53, 1.08)	
Stimulant use at prior visit	1.31 (0.69, 2.47)		NA	
***p < 0.05; **p < 0.01; ***p < 0.001**				

4. Discussion

This study examined the nature, timing, and predictors of changes in opioid and stimulant use among FSW living with HIV in eThekwini, South Africa. Overall, there was a high burden of opioid and stimulant use among FSW living with HIV in eThekwini, with 454 FSW (58.4%) reporting any opioid and/or any stimulant use during the follow-up period. Opioid use and abstinence from opioids, respectively, were more stable among FSW than stimulant use and abstinence from stimulants over the trial period. Time-to-event analyses revealed that opioid use at a prior study visit predicted stimulant initiation and vice versa, highlighting a linkage between these substance use types in this population. These analyses also demonstrate the contribution of demographic and psychosocial factors — namely age, arrest history, social

support, and stigma — to substance use patterns; these factors should be carefully considered as substance use interventions are developed and deployed for FSW in South Africa.

The trend toward concurrent opioid and stimulant use over time in this population suggests that syndemic opioid and stimulant use may serve a practical purpose for FSW. This may include using stimulants to manage periods of withdrawal from opioids or using opioids to “come down” from the effects of stimulants (Fredericksen et al., 2024; Palmer et al., 2020; Shannon et al., 2011). These findings are consistent with prior research demonstrating high prevalence of concurrent opioid and stimulant use among FSW in South Africa (Needle et al., 2008; Rosen et al., 2024) and globally (Nestadt et al., 2022; Shokoohi et al., 2018) and are concerning given the growing body of evidence showing that concurrent opioid and stimulant use considerably elevates overdose risk (Bazazi et al., 2015; Fine et al., 2022; Palis et al., 2022). Additionally, various studies have shown that people who use both opioids and stimulants are less likely to seek treatment for opioid use (Cook et al., 2023; Frost et al., 2021) and generally have poorer opioid use disorder treatment outcomes (Castillo et al., 2023; Frost et al., 2021; Williamson et al., 2006) than people who use opioids alone. A cross-sectional latent class analysis of polysubstance use profiles in the full *Siyaphambili* study population at baseline found that FSW who used both opioids and stimulants were significantly more likely to exhibit HIV viremia and report experiencing homelessness, HIV stigma, and physical and sexual violence victimization than FSW with other substance use profiles, signaling that FSW with this polysubstance use profile are marginalized in ways that may compound the detrimental impact of substance use on their HIV outcomes (Rosen et al., 2024).

Substance use interventions targeted to the needs of FSW in South Africa could also improve HIV care engagement and retention in this population. Prior work in sub-Saharan Africa and elsewhere has found that reductions in substance use are associated with better HIV care outcomes (Madhombiro et al., 2020) and that engagement in substance use treatment improves ART adherence (Nosyk et al., 2015). Despite evidence that integrating substance use treatment and HIV care has the potential to greatly improve ART uptake among people who use drugs in sub-Saharan Africa (Hassan et al., 2019), South African healthcare providers have identified several barriers to care integration, including low substance use treatment literacy among patients and providers (Kaswa and De Villiers, 2023; Magidson et al., 2019) and anticipated and enacted substance use stigma from providers (Magidson et al., 2019). Internalized stigma was a strong inverse predictor of opioid cessation in the present study, further highlighting the link between stigma and substance use and the importance of addressing stigma as a barrier to treatment engagement. People who use drugs and are living with HIV in South Africa have indicated that they would appreciate the option to receive peer-led HIV and substance use treatment interventions, highlighting the potential role of trained peer mentors in improving HIV and substance use treatment engagement among FSW in this population (Magidson et al., 2019). This is also consistent with results from the present study, where high social support from family, friends, and peers was the only significant predictor of stimulant cessation.

This study has several limitations. First, a constraint of time-to-first-event analyses is that individuals are "dropped" from the analyses at the time of their first substance use initiation or cessation. While lasagna plots enabled us to visualize whether individuals change their substance use patterns multiple times over follow-up (Figure 1) and descriptively characterizing individual substance use trajectories allowed us to determine how many FSW reported inconsistent or relapsing substance use (Table S1), the time-to-event analyses used to assess predictors of substance use changes did not distinguish between individuals who sustained substance use initiation or cessation and those who did not. Second, all covariate and substance use measures in this study were self-reported and thus are subject to social desirability and recall biases. There are few studies assessing the validity of self-reported substance use outcomes among women in countries across sub-Saharan Africa. One study conducted with men in South Africa found low agreement between self-reported methamphetamine use and rapid diagnostic tests for methamphetamine use, with self-reports underestimating the true prevalence of methamphetamine use (Arfer et al., 2018). This suggests that self-reporting may underestimate the actual prevalence of illicit drug use in other populations in South Africa, especially FSW who confront profound, overlapping stigmas attributed to occupation, HIV status, and substance use. Third, we did not measure the frequency or magnitude of illicit drug use in this population, assess FSWs' experiences with harmful consequences of substance use (e.g. overdose), or assess whether FSW have previously accessed harm reduction services or substance use treatment, limiting our understanding of the prevalence of harmful substance use and substance use service engagement among FSW in South Africa. While previous qualitative research among FSW in eThekwini has demonstrated that FSW report daily or near-daily illicit drug use at the request of clients and pimps or to cope with psychological stress (Parmley et al., 2022), it is unclear how prevalent these experiences were in the *Siyaphambili* cohort. To better guide the design and delivery of FSW-tailored substance use services, future studies should quantify the frequency and magnitude of and outcomes associated with illicit drug use using validated instruments like the ASSIST screening tool (Humeniuk et al., 2010) among FSW across sub-Saharan Africa. Lastly, this study was conducted among a population of non-virally suppressed FSW living with HIV in eThekwini, South Africa, and patterns of substance use in this population may differ from those observed among FSW who are virally suppressed, do not have HIV, or live and work in environments with different drug markets or substance use patterns. Rates of past-month hazardous alcohol and illicit drug use among FSW living with HIV in eThekwini were lower in cross-sectional analyses including the full *Siyaphambili* cohort at baseline (Rosen et al., 2024), indicating that FSW in this population who were virally suppressed at baseline may use substances at lower rates or exhibit different substance use patterns than those who were not. Additionally, substance use patterns may differ between FSW who attended two or more study visits and were included in these time-to-event analyses and FSW who only attended one study visit, even though baseline rates of past-month hazardous alcohol and illicit drug use were similar between the two groups (Table S2).

The substance use patterns and predictors identified through this analysis could have important implications for substance use interventions geared toward FSW living with HIV in South Africa. In particular, the trend toward concurrent opioid and stimulant use among FSW highlights a

need for substance use interventions that integrate harm reduction approaches to both opioid and stimulant use, recognizing also that one often leads to the other. Prior work has shown that FSW in South Africa have high interest in substance use treatment but lack awareness of (Myers et al., 2014; Wechsberg et al., 2009) or financial and geographic access to (Myers et al., 2010) substance use treatment options. However, substance use treatment and harm reduction interventions deployed among other FSW populations (Johnson et al., 2023) and among South African women living with HIV (Petersen Williams et al., 2020) have been successful at reducing substance use, reducing risky substance use behavior (e.g. injection drug use and solitary drug use), and improving other health outcomes. Qualitative work could further elucidate FSWs' perceptions of substance use treatment and harm reduction services, as well as the circumstances surrounding changes in FSWs' substance use patterns and the impact of psychosocial factors on substance use. The integration of harm reduction services and HIV programming for FSW is needed, and these efforts should be community centered. Further, consideration of how HIV treatment support strategies are impacted by substance use will be critical to make the case to HIV programs and funders that addressing these cross-cutting needs is critical to achieving the desired programmatic impact.

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Data availability statement:

Data are available upon reasonable request to the corresponding author.

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Conflicts of interest:

The authors have no conflicts of interest to disclose.

Author declarations:

We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Highlights:

- Opioid and stimulant use are prevalent among female sex workers in South Africa
- Opioid use at prior study visit predicts stimulant initiation and vice versa
- Psychosocial factors (e.g. stigma) predict substance use changes over time

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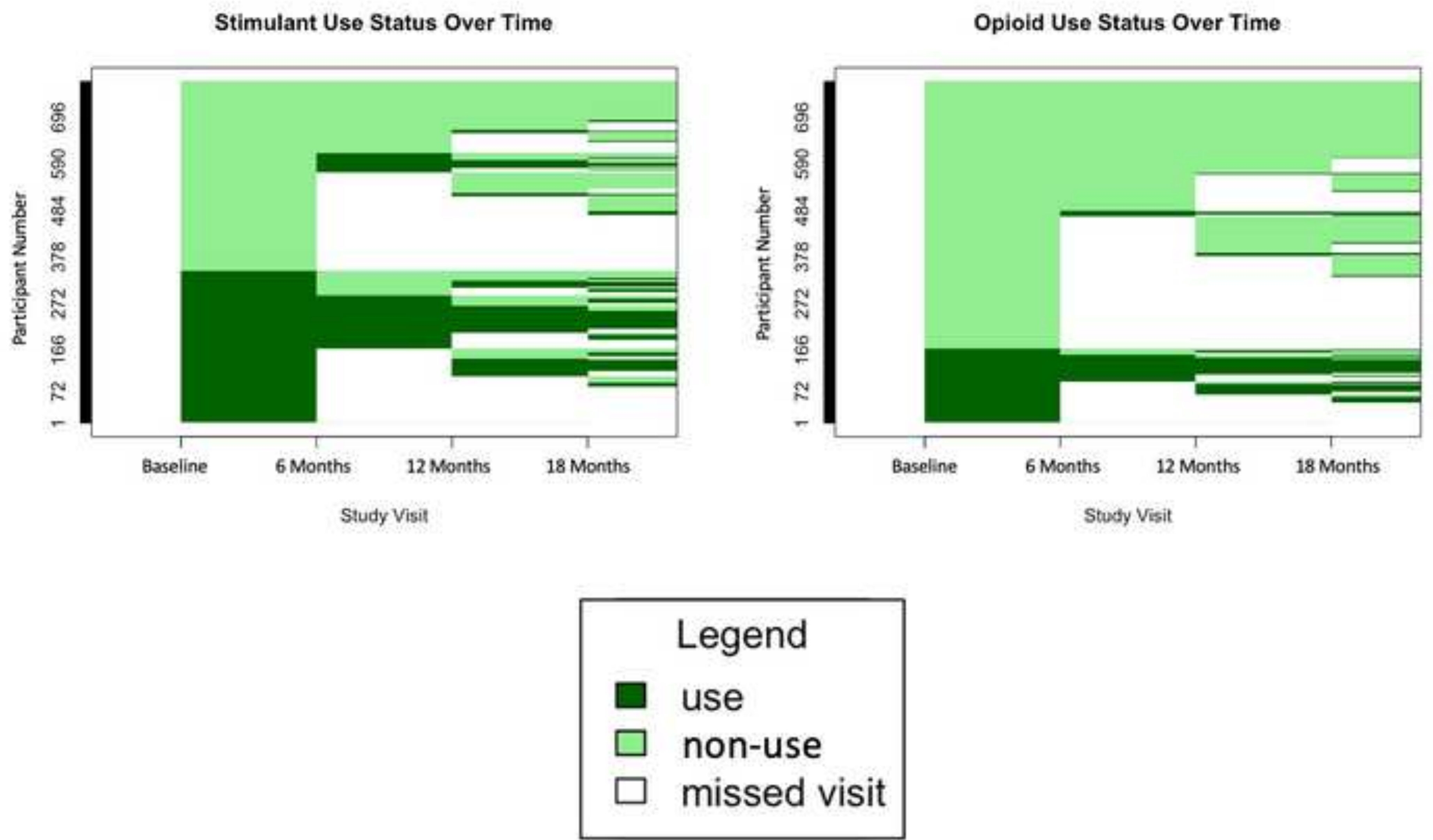

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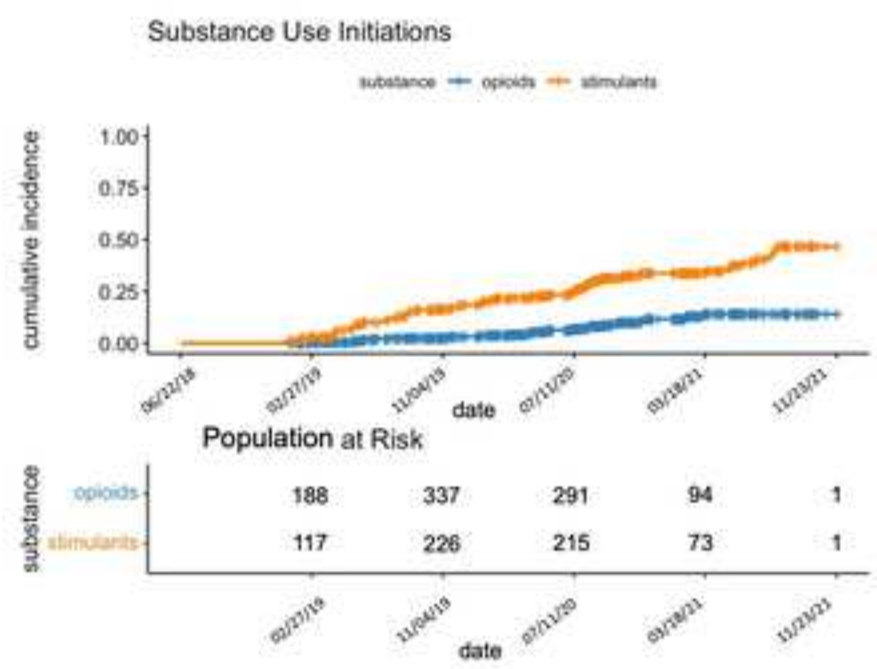

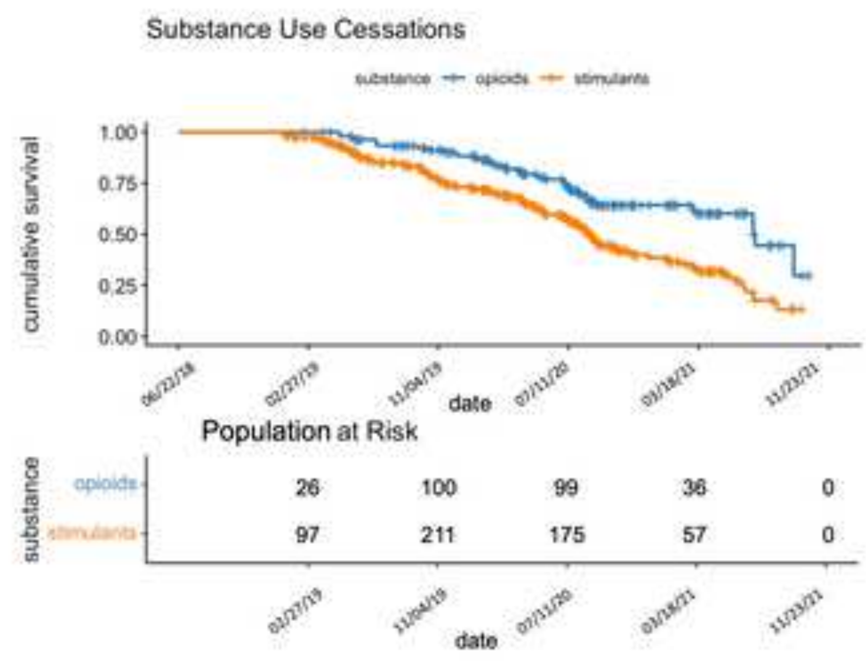

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Figure 1: Lasagna plots depicting individual trajectories of opioid and stimulant use over follow-up among FSW in the *Siyaphambili* cohort randomized to an HIV treatment support intervention at baseline (n = 777).

Figure 2a: Cumulative incidence of substance use initiations among FSW in the *Siyaphambili* cohort who provided information on recent substance use at two or more study visits. Curves depict opioid (n = 446) and stimulant initiation (n = 307) among FSW not using these substances at baseline. Population at risk reflects the total number of FSW under follow-up and at risk for substance use initiation on each date. **2b: Cumulative survival curves depicting substance use cessations among FSW in the *Siyaphambili* cohort who provided information on recent substance use at two or more study visits.** Curves depict opioid (n = 124) and stimulant (n = 263) cessations among FSW using these substances at baseline. Population at risk reflects the total number of FSW under follow-up and at risk for substance use cessation on each date.

Figure S1: Lasagna plots depicting individual trajectories of opioid and stimulant use over time (n = 777), stratified by baseline use of other substances.