



HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2024 May 01.

Published in final edited form as:

AIDS. 2023 May 01; 37(6): 977–986. doi:10.1097/QAD.0000000000003500.

Longitudinal patterns of initiation, persistence, and cycling on PrEP among female sex workers and adolescent girls and young women in South Africa, 2016–2021

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Abstract

Objective—Female sex workers(FSW) and adolescent girls and young women(AGYW) face a disproportionately high risk of HIV in South Africa. Oral PrEP can avert new infections, but its effectiveness is linked to consistent use. Early discontinuation of PrEP in this population is high, but less is known about longitudinal patterns of PrEP use, including patterns of re-initiation and cycling.

Design—Longitudinal descriptive analysis of routine program data.

Methods—Between 2016–2021, 40,681 FSW and AGYW initiated PrEP at TB HIV Care, the largest PrEP provider to this population in South Africa and were included. Using survival analyses and group-based trajectory modeling, we described patterns of initiation, discontinuation, re-initiation, and cycling.

Results—Total initiations increased over the life of the program for both FSW and AGYW. About 40% of FSW(0.41, 95% CI [0.40–0.42]) and AGYW(0.38, 95% CI [0.37–0.38]) remained on PrEP at 1-month. FSW were more likely to restart PrEP, however less than 10% restarted PrEP within a year of initiation. Three latent trajectory groups of PrEP use were identified for FSW(low use, early cycling, and ongoing cycling) and two for AGYW(low use and ongoing cycling). Persistence was negatively associated with initiation among AGYW, but there was no clear relationship among FSW. Those initiating later in the program and older women had a reduced risk of discontinuation.

Conclusions—Persistence on PrEP was low, but cycling on and off PrEP was common, with early missed visits and inconsistent, but ongoing use. A push to increase PrEP initiations needs to factor in readiness and persistence support, to achieve public health impact.

Keywords

HIV prevention; PrEP; female sex workers; adolescent girls and young women; survival analysis; routinely collected data; South Africa

INTRODUCTION

HIV incidence is disproportionately high among adolescent girls and young women (AGYW) ages 15–24 years old and female sex workers (FSW) in South Africa. Young women make up only 8% of South Africa's population but account for approximately one third of the 230,000 new infections reported annually.^{1,2} Further, as many as 60% of FSW are estimated to be living with HIV. The incidence rate in younger FSW is approximately 13.2 per 100 person years.³ While AGYW and FSW are often treated as separate groups both programmatically and in research settings, they share many risk factors for HIV acquisition, including age-disparate relationships, difficulty negotiating condom use, and economic instability.^{4–7} Little progress has been made toward mitigating their HIV risk, despite the significant need.²

Daily oral pre-exposure prophylaxis (PrEP) is an HIV prevention tool that has been shown to be between 79–90% efficacious among women when used consistently.^{8–10} Because it can be accessed without consent or approval from parents or partners as early as age 15, daily oral PrEP is a promising tool for addressing some of the unique structural prevention challenges facing young women.^{11,12} But early discontinuation and inconsistent pill-taking undermine its effective use.¹³ In prior demonstration studies in South Africa approximately half of PrEP users, including both AGYW and FSW, discontinued PrEP by 1-month.^{14–18} However, there are limited longitudinal data on PrEP use among women at high-risk who initiate and discontinue at least once.

The need for PrEP, unlike the need for treatment, can differ not only between individuals, but also within individuals over time.¹⁹ Risk of HIV may be episodic, and individuals may cycle on and off PrEP, coinciding with changes to perceived risk, sometimes referred to as risk-use alignment.^{19–21} Among women who initiate PrEP in South Africa, patterns of use following discontinuation are not well understood, but are important for informing program implementation and management, decisions about who should be initiated, and concerns about potential future resistance to antiretrovirals.¹⁹

Prior to 2022 and before full roll-out to public healthcare facilities, PrEP in South Africa was largely delivered through implementing partners, including NGOs and other non-profits that have experience providing health services to prioritized populations. As these programs are primarily donor-funded, these implementing partners have finite resources and staff, and increasing the number of patients who initiate PrEP may mean fewer per-client resources to support adherence and persistence. This relationship between number of people initiated on PrEP and PrEP persistence has not been studied.

The objective of this study was to examine patterns of PrEP initiation, discontinuation, re-initiation, and cycling among FSW and AGYW who initiated PrEP through TB HIV Care

(THC), the largest PrEP provider to women in South Africa. In addition, we described the relationship between PrEP persistence and age and year of initiation, and the program-level relationship between initiation and persistence.

METHODS

Study Population and Setting

THC is a South African non-profit that provides integrated health services to populations at high risk, including HIV testing, reproductive health services, and STI syndromic screening and treatment. TB HIV Care has been providing PrEP to FSW since 2016 and AGYW since 2018. Data for this analysis come from site-level (district unit of administration) or clinic-level registers that track PrEP use over time.

FSW were served by nine sites in five provinces across South Africa: KwaZulu-Natal (eThekweni, uMgungundlovu), Mpumalanga (Ehlanzeni, Gert Sibande, Nkangala), North West (Kenneth Kaunda, Ngaka Modiri Molema), Eastern Cape (OR Tambo), and Western Cape (Cape Town). AGYW were served by four sites in three provinces: KwaZulu-Natal (eThekweni, uMgungundlovu), Gauteng (Ekurhuleni), and Western Cape (Cape Town). The program records information on individual clinical encounters, or any time a client comes in to receive services, on paper forms and stores these forms in locked and secure file cabinets. Data capturers then enter these data into registers at least once a week for each site. The secondary use of programmatic data for these analyses was reviewed by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board and the University of Western Cape Research Ethics Committee; a waiver of informed consent was provided, as all of the data were deidentified.

We included FSW and AGYW who accessed health services from THC (e.g. HIV testing, sexual and reproductive health services) and who tested negative for HIV. Because clients in this study were categorized as FSW or AGYW according to the program through which they were recruited and from where they received services, some individuals who were older than 24 years old were categorized as AGYW. TB HIV Care generally provides services to FSW from known sex work venues, including brothels, bars, and street-based venues, and AGYW from locations where young women tend to congregate, like schools, community centers, and areas of commerce. AGYW served by TB HIV Care are at greater risk of HIV acquisition than AGYW more broadly, and may have age-disparate relationships, multiple partnerships, participate in transactional sex, or have unstable home environments and/or school attendance. Specific risk factors for HIV acquisition are documented using the Determined, Resilient, Empowered, AIDS-Free, Mentored and Safe (DREAMS) eligibility criteria. The study period included data from when PrEP was first made available through THC until the administrative censoring date (June 2016-August 2021 for FSW and May 2018-September 2020 for AGYW). The administrative censoring date for AGYW is earlier than for FSW given a change in the structure of the AGYW PrEP registers, which precluded the inclusion of more recent data in these analyses.

Outcomes

The primary outcomes of interest for both FSW and AGYW included PrEP initiation, discontinuation, and re-initiation. PrEP initiation was defined as choosing to start oral PrEP (tenofovir/emtricitabine) and taking home a 1-month supply of pills. We defined the denominator for the proportion initiating PrEP as the number testing negative for HIV during the same month; this was the number of unique encounters, and women could have tested in more than one period. Among women who initiated PrEP, we defined discontinuation as two consecutive missed monthly PrEP visits, a client-initiated stop, or a provider-initiated stop. The discontinuation event was assigned to the first month of the two consecutive missed visits or the month of the client-initiated or provider-initiated stop. This definition of PrEP discontinuation is the one used by the program in alignment with PEPFAR reporting definitions.²² Re-initiation was defined as restarting PrEP within 12 months of an initial PrEP prescription, after a ≥ 2 month gap in PrEP (a discontinuation). PrEP cycling was defined as going in and out of different states of PrEP use (starting, stopping, and starting again).

Covariates

We also assessed woman's age and year of PrEP initiation (2016–2021) as potential covariates of PrEP discontinuation.

Statistical analyses

Initiation—We plotted the monthly proportion of HIV negative encounters who initiated PrEP over calendar time, by population (FSW and AGYW) and stratified by site. Data on the number of HIV negative encounters were missing for 2% of FSW months (6/337) and 20% of AGYW months (108/537). We assumed, based on discussions with THC program staff, that data were missing completely at random and excluded those months from our analyses.

Discontinuation—We examined time from PrEP initiation to discontinuation using Kaplan-Meier survival curves, by population and stratified by site. Individuals were censored after 12 months of follow-up based on data on continuation being captured in registers for the 12 months following initiation or at the end of the study period (administrative censoring). During the study period, the program switched to multi-month dispensing after the first month to alleviate the burden of having to return monthly (December 2019 for FSW and March 2020 for AGYW), meaning that women were seen at 1-month and thereafter at 4-months, 7-months, etc. After the switch to multi-month dispensing, a woman was recorded as persistent on PrEP in the intervening months if she had the supply of PrEP for those months in her possession.²² Women were recorded as discontinued if they missed a refill appointment.

Re-initiation—To explore patterns of re-initiation, we estimated time from PrEP discontinuation to re-initiation using the complement of Kaplan-Meier survival function to estimate the cumulative incidence of re-initiation, by population and stratified by site. Individuals were censored at 12 months following their initial initiation due to availability of data.

Group-based trajectory modeling—We used group-based trajectory modeling to describe monthly PrEP use over the one year period following PrEP initiation. Individual trajectories of PrEP use were used to model latent groups of individuals whose outcomes follow a similar pattern over time. Those individuals who were on PrEP in a given month were coded as “1”, while those who were not on PrEP were coded as “0.” We considered linear, quadratic, and cubic specifications for the shape of each trajectory group and options for the number of groups (between 2–6) and systematically compared each permutation using model diagnostics. The final models were selected to optimize Bayesian Information Criteria (BIC), entropy, and alignment with existing models of PrEP persistence in the literature.^{23,24}

Correlates of discontinuation—We also described correlates of discontinuation. We plotted 1-month persistence against the total number of initiations in a given month, stratifying by population and site (to examine the hypothesis that persistence decreases with a greater number of initiations). We also formally assessed the relationship between persistence and initiation using linear regression models for each population, adjusting for site and scaling the number of initiations by 100. We estimated hazard ratios for discontinuation overall and looked at associations between hazard of discontinuation and site, age, and year of initiation using a multivariable complementary log-log regression model. We used a complementary log-log regression model, because while data are collected at discrete time points (monthly), the underlying hazard of discontinuation, which could occur at any point during the month, is continuous.

All analyses were conducted using Stata 14.2 (StataCorp, College Park, Texas, USA).

RESULTS

Overall, 40,681 individuals initiated PrEP at THC during the study period and were included in these analyses, including 12,581 FSW and 28,100 AGYW. Among FSW, the two largest sites were eThekweni (n=3,268, 26%) and uMgungundlovu (n=2,919, 23%). Among AGYW, the two largest sites were Cape Town (n=9,660, 34%) and uMgungundlovu (n=11,866, 43%). Over one third (n=10,622, 38%) of AGYW were adolescents (15–18 years old). A large proportion of both populations was between the ages of 19 and 24 years old: about 2 of 5 FSW (n=4,846, 39%) and more than half of AGYW (n=15,824, 56%)(Table 1).

Initiation

The number of initiations increased for both populations, from 302 in 2016 to its highest value of 4,618 in 2020 for FSW and 1,286 in 2018 to 14,489 in 2020 for AGYW(Table 1). Across the study period, approximately 19% (12,581/65,782) of negative HIV test encounters resulted in an initiation among FSW, compared with 55% (28,100/51,436) of negative test encounters among AGYW. Among FSW, the proportion of initiations increased over time, with a monotonic increase beginning in 2018(Figure 1). At sites that began providing PrEP later in calendar time, the proportion of HIV negative encounters among FSW who initiated was generally higher early on, and there was not a clear increasing trend in initiations, specifically for Ehlanzeni, Ngaka Modiri Molema, and Kenneth Kaunda(Appendix Figure 1). Among AGYW, while there was an observed increase

in the proportion of initiations over time, this increase was not statistically significant and there was substantial heterogeneity across sites(Figure 1). At the two largest sites (Cape Town and uMgungundlovu), there was a clear increase in initiations over time for both populations, while at one smaller site (eKurhuleni) there was a dramatic decrease. Further, one site only contributed 4 months of observations due to missing data(Appendix Figure 1).

Discontinuation

The 40,681 individuals who initiated PrEP during the study period contributed 90,377 person-months to the analysis of time to discontinuation. Both populations had low persistence, with 41%(95% CI: 40%–42%) of FSW and 38%(95% CI: 37%–38%) persisting at 1-month(Figure 2). Over the 12 months of follow-up, AGYW experienced a slightly earlier drop-off(Figure 2). There were substantial differences in PrEP persistence across sites(Figure 2), particularly for AGYW.

Re-initiation

A total of 2,131 individuals initiated for a second time within 12 months of a first PrEP initiation. The marginal probability of reinitiation was 5%, with a greater proportion of FSW($n=1,146$, 9%) reinitiating compared with AGYW($n=985$, 3%)(Figure 3). Among FSW, the greatest number of re-initiations occurred at eThekweni and Cape Town, and among AGYW, the greatest number occurred at uMgungundlovu(Appendix Table 1).

Group-based trajectories of PrEP use

We identified three latent trajectory groups for FSW(BIC: $-37,369$, Entropy: 0.97, Shape parameter: cubic) and two for AGYW(BIC: $-73,738$, Entropy: 0.95, Shape parameter: quadratic). (Figure 4)

For FSW, we identified three groups, which we defined as “limited use,” “early cycling,” and “ongoing cycling” based on the observed trajectories. The majority(57%) of FSW were in the Limited Use group: 5% were on PrEP at one month and 0.1% were on PrEP in any subsequent month. Twenty-two percent of FSW were in the Early Cycling group. In this group, 76% were recorded as on PrEP at one month and this increased at two months to 95%. By 5 months following initiation, less than 0.5% were on PrEP. Twenty-one percent of FSW were in the Ongoing Cycling group, of whom, 62% were on PrEP at one month, 71% at 4 months, 51% at 7 months, and 27% at 10 months(Figure 4).

For AGYW, we identified two groups, which we defined as “limited use” and “ongoing cycling.” Similar to FSW, the majority were in the Limited Use group(66%) and about a third were in the Ongoing Cycling group(34%). Among AGYW in the Limited Use group, 7% were on PrEP at one month and 2% were on PrEP in any subsequent month. Among AGYW in the Ongoing Cycling group, 85% were on PrEP at one month, 36% at 4 months, 16% at 7 months, and 7% at 10 months.(Figure 4)

Correlates of discontinuation

Among FSW, there was no definitive relationship between 1-month persistence and the number of initiations. Among AGYW, 1-month persistence was negatively associated with

an increase in initiation, and this pattern was seen across all sites (Appendix Figure 2). An increase of 100 initiations per month was associated with a 2% decrease in 1-month persistence (-0.02 (95% CI: $-0.03, -0.01$).

For both populations in the adjusted models, older age was associated with lower likelihood of discontinuation. Among FSW, hazard of discontinuation was higher in 2017 and 2018 compared with 2016, but lower in all subsequent years (2019, 2020, and 2021) compared with 2016. Among AGYW, hazard of discontinuation was higher in 2019 and lower in 2020 compared with 2018. (Appendix Table 2).

DISCUSSION

In this study, we described longitudinal patterns of PrEP use among over 40,000 young women in South Africa participating in a real-world PrEP program. The number and proportion of women who initiated PrEP increased each year. The increase in initiations was sustained even during the early part of the COVID-19 pandemic. However, 1-month PrEP persistence was only 41% among FSW and 38% among AGYW. Re-initiations were more common among FSW than AGYW, but represented less than 10% of all individuals. The majority of both FSW and AGYW experienced “limited use” of PrEP, with few returning after the first month, but close to half of FSW and one third of AGYW experienced some form of cycling.

Across the study period, 19% of negative tests among FSW and 55% among AGYW resulted in initiation. Some possible explanations, as provided anecdotally by those delivering PrEP, for the lower levels of initiation seen among FSW include 1) FSW have been using condoms as a trusted prevention method and may not see the need to change or supplement this and 2) FSW experience unstable housing, which may challenge daily pill-taking.²⁵ Additionally, because women can test multiple times each year (FSW are recommended to test quarterly) and because it includes those who are already on PrEP, the denominator overestimates the number eligible, and the proportion initiating in a given month is likely an underestimate of the proportion who ever initiated PrEP. Data on the proportion of eligible women who initiate PrEP in similar settings are limited. For FSW, PrEP uptake was similar to what was documented in a study of Zimbabwean FSW, including the increase in the proportion of initiations over time and the durability of increases to the COVID-19 pandemic.²⁶ The proportion of eligible AGYW who initiated PrEP in our study was lower than in some studies conducted in highly-controlled trial settings and/or in population groups with potentially different motivations for PrEP (e.g. women engaged in antenatal care).^{16 27} However, the proportion of eligible AGYW initiating PrEP in the present study was comparable, if not slightly higher, to similar observational studies and demonstration projects.^{28–30}

Similar to what has been previously demonstrated in varied settings in sub-Saharan Africa, persistence on PrEP among both FSW¹⁴ and AGYW^{15,31,32} was low. A recent study of similar programmatic data from the DREAMS Initiative in Kenya found that about 37% of 1259 AGYW persisted on PrEP at 3 months.³¹ This study of DREAMS AGYW data also identified heterogeneity across program sites and found that older age was associated with

improved persistence.³¹ Another study of three JHPIEGO supported programs in Kenya, Lesotho, and Tanzania found that about half of the close to 50,000 individuals initiating PrEP ever returned.²¹

In our study, only 9% of FSW and 3% of AGYW re-initiated within one year. Though the present data source does not have data on motivation to use PrEP or risk perception, it is possible that FSW had a more established understanding of and reason for using PrEP and therefore returned at a higher frequency to restart.^{33,34}

Many in our study population experienced irregular engagement in PrEP services which, based on our latent trajectory models, we defined as “early cycling” and “ongoing cycling.” While the data on 1-month persistence are disheartening, women are continuing to engage in PrEP use after this initial discontinuation. If we can distinguish between those women who may end up displaying patterns of early or ongoing cycling compared with those who have limited to no use, programs can implement differentiated systems of support or even consider making changes in who to initiate and when to do so. There have been few studies of PrEP use trajectories, and these have been in different populations, including racial and ethnic minorities in Chicago, USA²⁰ and gay men in New South Wales³⁵, or have used PrEP adherence as the primary outcome rather than PrEP persistence. In the two studies conducted in high-resource settings^{20,35}, those who belonged to the “sustained use” group, or the “good” or “excellent” adherence groups made up the majority of the study population. This is very different from what we observed in our study population. This suggests that PrEP use trajectories may also be influenced by sociostructural, economic, and political factors. In a study of trajectories of adherence among 200 young women in a research setting in Cape Town, the authors identified two groups: 48% with low adherence and 52% with high early adherence.²⁴ In this study, individuals initiating PrEP received regular adherence counseling.²⁴ The latent groups identified do align with what we found among AGYW, but a larger proportion of our study population, closer to two-thirds, were in the low use group. There are no prior data on trajectories of PrEP use among FSW.

While the program created and utilizes a process to ensure some form of PrEP readiness prior to initiation in line with the South African National Guidelines¹², further resources may be needed to comprehensively address multifactorial barriers^{36,37} to PrEP use, including patient-related barriers^{36,38,39} (awareness of PrEP, HIV and PrEP-related stigma, and readiness), clinic-level barriers^{36,39,40} (provider knowledge, adequate and friendly communication with clients, delivery and availability of refills), community-level barriers^{37,39} (social pressure, lack of awareness among partners, parents, and the community, and potential violence). Even with tailored adherence support, without a clear understanding and readiness on the part of the user in the context of other social and structural barriers, PrEP pills will go unused at a non-trivial cost to the program. There is a risk of the development of HIV drug resistance,⁴¹ with women starting on PrEP, but not maintaining a therapeutic dose.

There are some limitations of these analyses. First, individuals were characterized as FSW or AGYW based on which of the two programs they received services from. This decision led to 1608 women who were 25 years and older being placed in the AGYW group (5.7%,

1608/28,100). While these individuals would not normally be characterized as AGYW, often described as those 15–24 years old, we felt that this categorization was most appropriate as these women were being served by a program with AGYW as the intended target population. Second, for the analysis examining the proportion initiating over calendar time, data were missing for approximately 20% of the site-months among AGYW. Data on the number of women testing negative each month come from aggregated statistics captured in program registers. This indicator was not required for reporting to donors and was not always regularly inputted into the program register. The individual-level data feeding into these aggregate statistics were captured on paper logs, and where possible, we went back to obtain these numbers; there were some months for which these paper logs were no longer available. While we believed these data to be missing completely at random, we could not verify this assumption because of limited data availability, and some bias may have been introduced due to missing data. Finally, during the study period, the program shifted from monthly to multi-month dispensing. The details regarding this change have been described previously.²² For those months in which the woman had PrEP in her possession, but did not need to return for a visit, the PrEP register still documented that woman as being on PrEP. We therefore chose to keep our unit of analysis as monthly ability to use PrEP to ensure comparability across the years. Our measure of PrEP persistence should be comparable before and after the institution of multi-month dispensing, but if the measure of PrEP persistence was implicitly used as a proxy for actual pill-taking, it is possible that it would take longer to detect stopping of use with multi-month dispensing (would not know that they had been off PrEP until next scheduled pick-up visit). It should be noted that our measure of persistence does not imply adherence, which may be, and likely is, lower for many people. These results represent a best-case scenario for adherence given the fact that not all those who pick up their refills are taking pills at the level necessary to confer protection.

CONCLUSION

The results from these analyses reinforce that persistence on PrEP among young women at high-risk for HIV is low. We demonstrated that cycling on and off PrEP is common, with early missed visits and inconsistent, but ongoing use. The traditional approach to capturing and documenting formal discontinuation and re-initiation events may be obfuscating these important patterns of PrEP use, which are varied and may correspond to changes in actual or perceived risk or may be due to barriers to accessing PrEP. While we were unable to unpack individual-level characteristics of who specifically is represented in the different trajectory groups, better understanding of these varying patterns of PrEP use, including early and ongoing cycling, may help us tailor who is immediately started on PrEP and strategies to improve and support persistence. A push to start as many as possible on PrEP without consideration of 1) readiness or ability to stay on PrEP, and 2) a plan for providing clear persistence support, means that many, even a majority, of these initiations will prove futile.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of support for this manuscript include:

National Institute of Mental Health: F31MH124458 (PI: Rao)

National Institute of Mental Health: R01MH121161 (PI: Schwartz)

National Institute of Allergy and Infectious Diseases: R01AI170249 (PI: Baral)

National Institute of Mental Health: K01MH129226 (PI: Rucinski)

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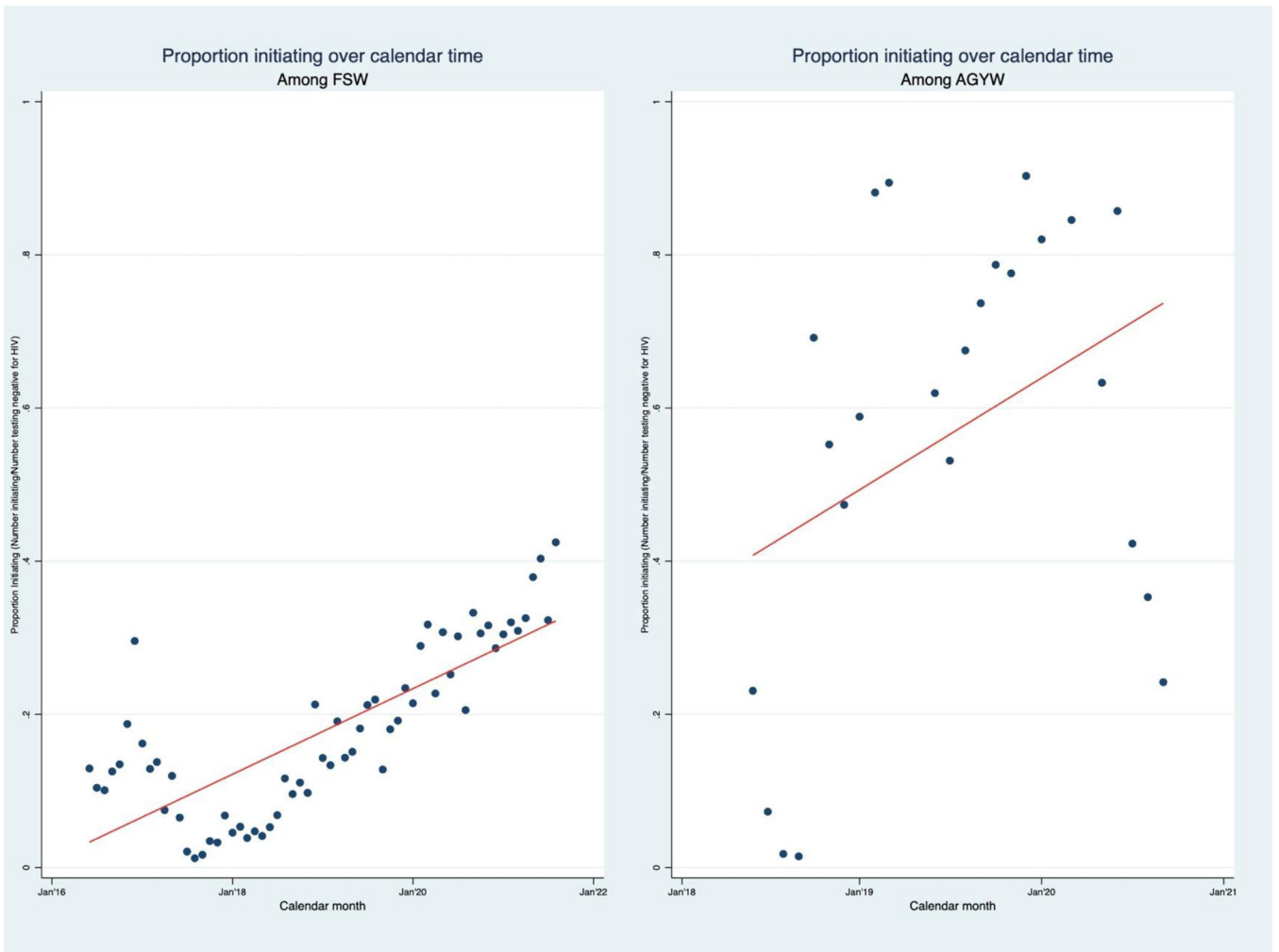


Figure 1. Proportion of eligible HIV negative encounters initiating PrEP over time among female sex workers and adolescent girls and young women at TB HIV Care (2016–2021)

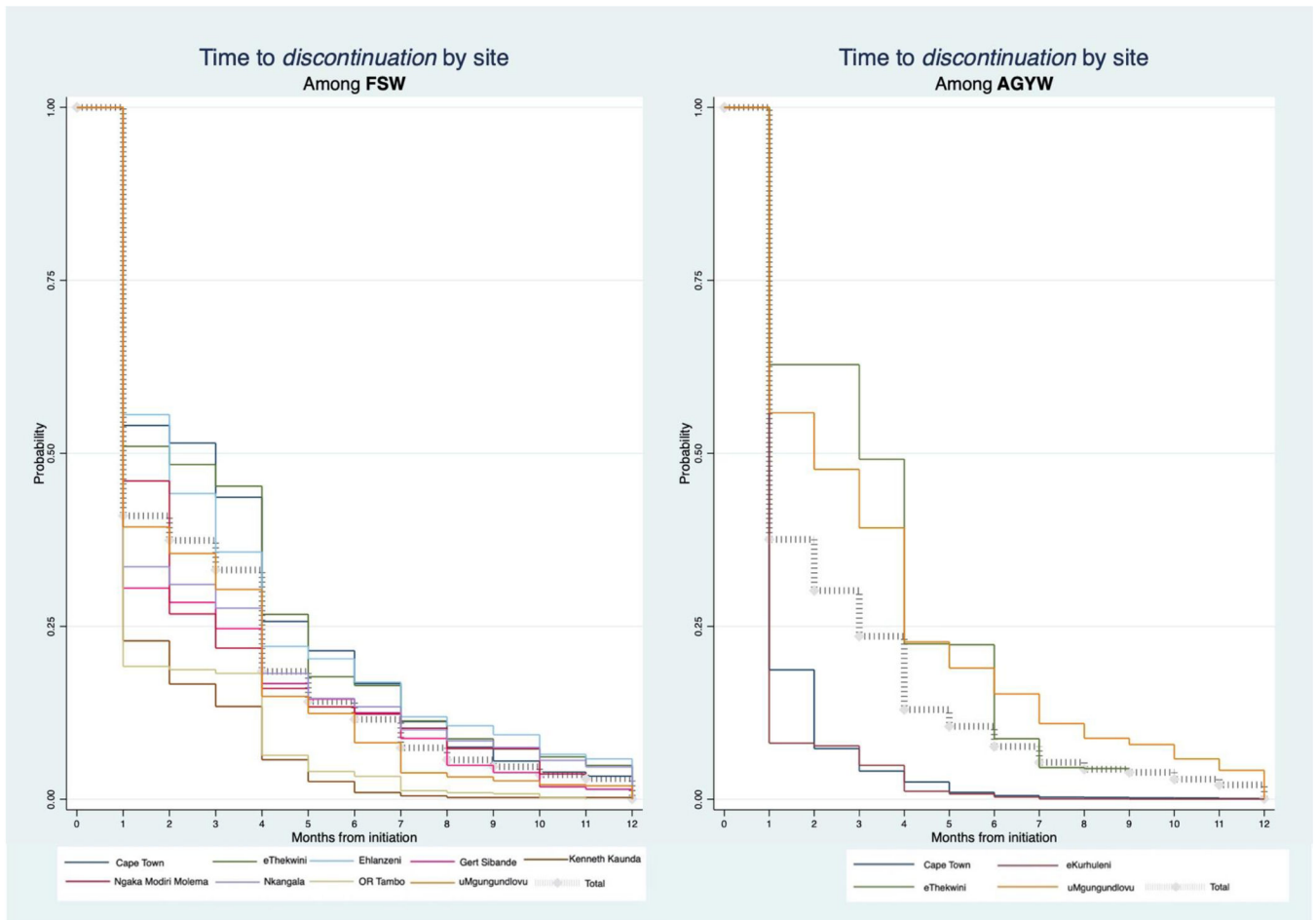


Figure 2. Kaplan-Meier survival curves of the time from initiation to first discontinuation by site among female sex workers (n=12581) and adolescent girls and young women (n=28100) who initiated PrEP between 2016 and 2021 at TB HIV Care

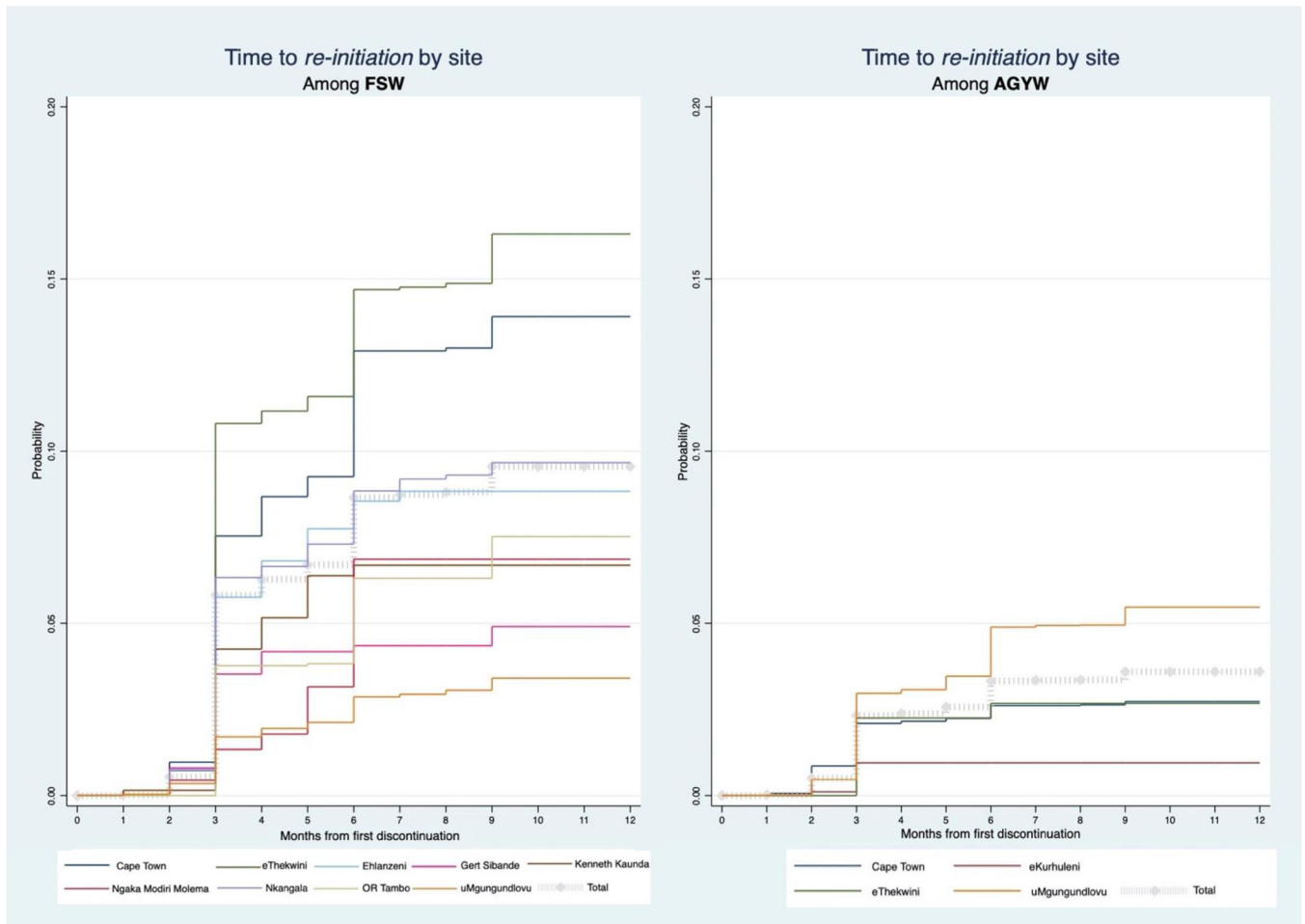


Figure 3. Cumulative incidence curves of the time from discontinuation to re-initiation by site among female sex workers (n=12,581) and adolescent girls and young women (n=28,100) who initiated PrEP between 2016 and 2021 at TB HIV Care

Average trajectory groups of persisting on PrEP

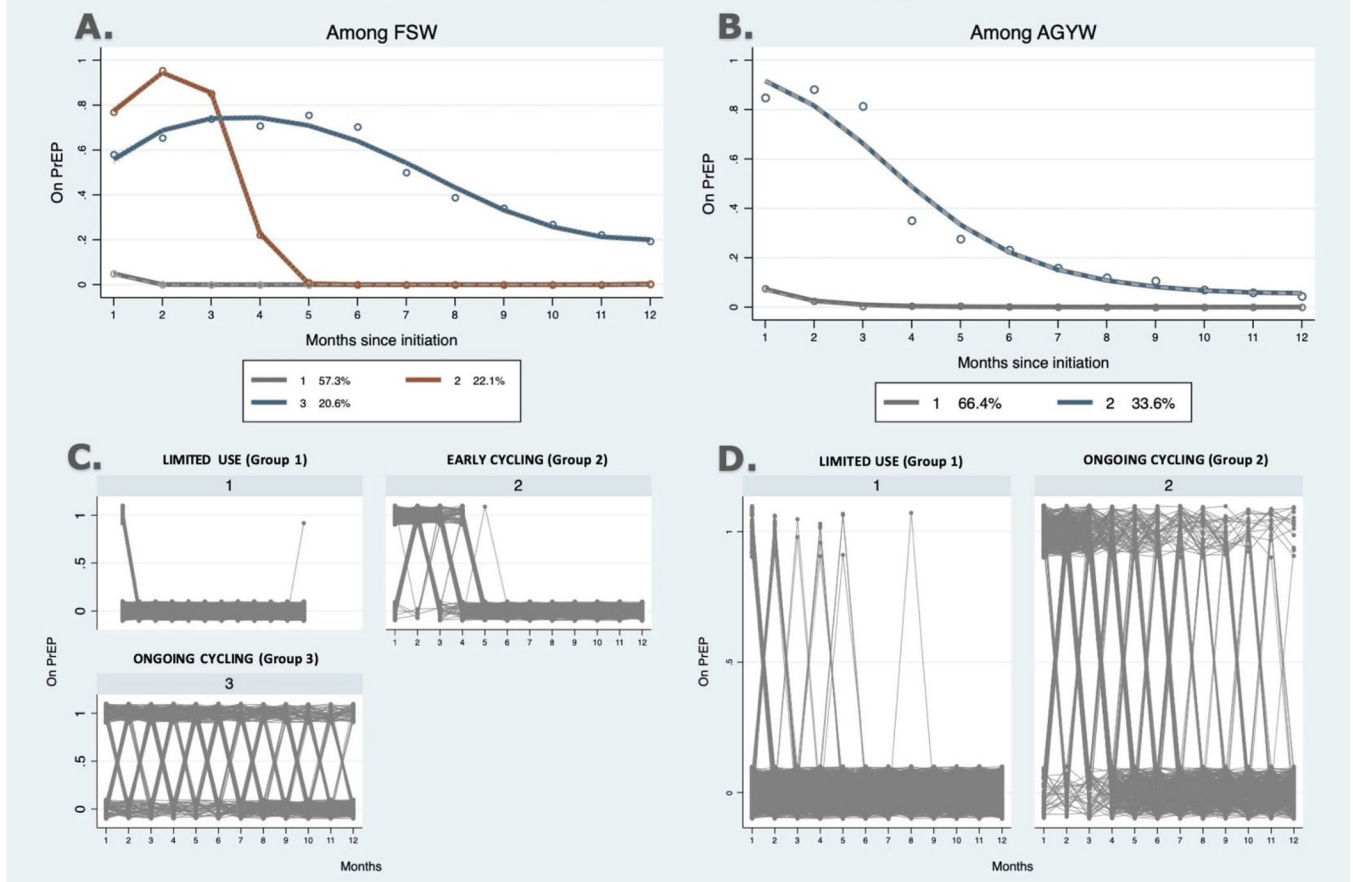


Figure 4. Average trajectory groups based on latent groups of persisting on PrEP from group-based trajectory models, stratified by FSW (a) and AGYW (b) populations and individual trajectories of PrEP use for a random sample of 1000 individuals drawn from 12,581 FSW (c) and 1000 drawn from 28,100 AGYW (d)

Characteristics of female sex workers (FSW) and adolescent girls and young women (AGYW) initiating PrEP through TB HIV Care between 2016 and 2021

Table 1.

	Female sex workers N=12,581	Adolescent girls and young women N=28,100
Site		
Cape Town	12% (1,486)	34% (9,660)
eKurhuleni		13% (3,684)
eThekweni	26% (3,268)	10% (2,890)
Ehlanzeni	6% (813)	
Gert Sibande	5% (629)	
Kenneth Kaunda	5% (659)	
Ngaka Modiri Molema	2% (226)	
Nkangala	8% (988)	
OR Tambo	13% (1,593)	
uMgungundlovu	23% (2,919)	43% (11,866)
Age		
15–18 years old	7% (939)	38% (10,662)
19–24 years old	39% (4,846)	56% (15,824)
25–34 years old	40% (5,039)	5% (1,318)
35 years old or older	14% (1,730)	1% (290)
Year of initiation		
2016	2% (302)	
2017	3% (348)	
2018	8% (962)	5% (1,286)
2019	25% (3,153)	44% (12,325)
2020	37% (4,618)	52% (14,489)
2021	25% (3,197)	