

**PRE-EXPOSURE PROPHYLAXIS FOR HIV PREVENTION (PrEP) AMONG YOUNG
WOMEN AT HIGH RISK FOR HIV IN SOUTH AFRICA: LONGITUDINAL PATTERNS
OF USE AND STRATEGIES TO IMPROVE PERSISTENCE**

by

Amrita Rao

A dissertation submitted to Johns Hopkins University in conformity with the
requirements for the degree of Doctor of Philosophy

Baltimore, Maryland

June 2022

© 2022 Amrita Rao

All Rights Reserved

ABSTRACT

Background. Adolescent girls and young women (AGYW) and female sex workers (FSW) make up a disproportionate share of HIV infections in South Africa. Oral pre-exposure prophylaxis for HIV prevention (PrEP) can prevent new infections, but low levels of persistence limit its real-world impact. We aimed to characterize patterns of PrEP use, including initiation, discontinuation, and cycling, and to identify implementation strategies that may improve PrEP persistence.

Methods. We worked with a South African non-profit, TB HIV Care, to create a cohort of AGYW and FSW eligible for PrEP using routinely collected data. First, we described persistence on PrEP among FSW in eThekweni using a discrete time-to-event survival analysis. Discontinuation was defined as a composite outcome based on 1) two months of not returning for PrEP, 2) client discontinuation, or 3) provider discontinuation. Second, we used discrete time-to-event survival analyses and group-based trajectory modeling to describe the longitudinal patterns of PrEP initiation, discontinuation, and re-initiation across both AGYW and FSW. Eligibility for PrEP initiation was defined as testing negative for HIV. Re-initiation was defined as a new PrEP initiation within 12 months of an initial PrEP prescription, following a 3-month gap in PrEP. Third, we used an interrupted time-series design to evaluate the impact of PrEP delivery strategies, including clinical mentoring for providers, SMS PrEP refill reminders and support texts, case management, and a loyalty rewards program, on 1-month PrEP persistence.

Results. Persistence at one month for AGYW (0.38, 95%CI [0.37-0.38]) and FSW (0.41, 95%CI [0.40-0.42]) was low. PrEP cycling was common, with close to half of

FSW (22% “Early Cycling”; 21% “Ongoing Cycling”) and one third of AGYW (34% “Ongoing Cycling”) experiencing some form of cycling during the year following initiation. SMS support and refill reminders and provider training had a positive impact on 1-month persistence among FSW.

Conclusions. PrEP-delivery programs have focused a large portion of available resources on promoting uptake; however, low PrEP persistence and inadequate understanding of cycling will undermine PrEP as a prevention tool. SMS support, refill reminders, and provider training show promise for improving immediate PrEP persistence, but strategies to augment these are needed for sustained PrEP use.

Primary Reader and Advisor: Catherine Lesko, PhD

Assistant Professor, Department of Epidemiology

Johns Hopkins Bloomberg School of Public Health

Non-Voting Member and Co-Advisor: Sheree Schwartz, PhD

Associate Scientist, Department of Epidemiology

Johns Hopkins Bloomberg School of Public Health

Thesis Reader and Sponsor of NIH F31 Award: Chris Beyrer, MD

Professor, Department of Epidemiology

Johns Hopkins Bloomberg School of Public Health

Thesis Reader: Susan Sherman, PhD

Professor, Department of Health Behavior and Society

Johns Hopkins Bloomberg School of Public Health

Thesis Reader: Cassandra Crifasi, PhD

Associate Professor, Department of Health Policy and Management

Johns Hopkins Bloomberg School of Public Health

ACKNOWLEDGEMENTS

This dissertation would not have been possible without the unwavering support of colleagues, friends, and family.

First and foremost, I would like to acknowledge and thank my Thesis Advisory Committee and some key faculty members. Thank you to Drs. Katie Lesko and Sheree Schwartz: I could not have asked for more intelligent, supportive, and thoughtful advisors. I am in awe not only of your work and your numerous accomplishments as academics, but also, more importantly, of who you are as people and all that you do. Thank you for your kindness and for always building me up. I can only hope that our work together continues for years to come. To Drs. Chris Beyrer and Jess Edwards, thank you for your commitment to my progress as a doctoral student and for being on my Thesis Advisory Committee. Thank you especially to Dr. Beyrer for serving as the primary Sponsor of my F31 award and for guiding me in the process of submitting and receiving my first grant. Thank you to Drs. Sherman and Crifasi for serving as both Thesis Readers and as members of my final oral exam committee, and for providing me with valuable feedback before critical milestones. And to Dr. Stefan Baral, thank you for the ongoing support and for providing me with opportunities to get involved. My time as a doctoral student was made much richer by the opportunities I had to get involved in COVID-19 related research, and this was largely made possible by Dr. Baral. To Drs. Becky Genberg and Kate Rucinski, thank you for helping me to navigate both research and professional obstacles.

Thank you to the Center for Public Health and Human Rights and colleagues at TB HIV Care (specifically Hlengiwe Mhlophe, Mfezi Mcingana, Jenny McLoughlin, Anje Pretorius, and Harry Hausler). I feel incredibly proud of the work that we have all been a part of and cannot imagine a better place to work or a better group of people.

To my writing accountability group, Kayte Andersen, Neia Prata Menezes, and Jean Olivier Twahirwa Rwema, you have become my forever friends. Your friendship and support have been invaluable to me; it is truly an honor to call you my peers.

Importantly, thank you to Laura Camarata, Fran Burman, and Matt Miller for keeping tabs on me and helping me to navigate the numerous steps of this PhD.

Thank you to Anuj for supporting me each and every day of this process and for being my person. Thank you to Vivek, Lily, Julian, and Asha for showing up and making me smile with the cutest photos of kiddo shenanigans. And finally thank you to my parents for everything you have done and everything you are.

TABLE OF CONTENTS

ABSTRACT	ii
ACKNOWLEDGEMENTS	v
TABLE OF CONTENTS	vii
LIST OF TABLES	ix
LIST OF FIGURES	xi
ABBREVIATIONS	xiii
CHAPTER 1: INTRODUCTION.....	1
HIV incidence in South Africa: young women at disproportionately high risk.....	1
Pre-exposure prophylaxis for HIV prevention (PrEP) is an efficacious tool to prevent new HIV infections	2
Persistence and adherence challenges.....	3
PrEP cycling	4
Implementation strategies to improve PrEP use	4
TB HIV Care and the use of routinely collected data.....	5
REFERENCES	6
CHAPTER 2: Persistence on oral pre-exposure prophylaxis (PrEP) among female sex workers in eThekweni, South Africa, 2016-2020	10
ABSTRACT	11
INTRODUCTION	13
METHODS.....	14
RESULTS	16
DISCUSSION	17
REFERENCES	27

CHAPTER 3: Longitudinal patterns of initiation, persistence, and cycling on PrEP among female sex workers and adolescent girls and young women across multiple program sites in South Africa, 2016-2021	30
ABSTRACT	31
INTRODUCTION	33
METHODS.....	35
RESULTS	40
DISCUSSION	45
CONCLUSION.....	50
REFERENCES	61
CHAPTER 4: The impact of implementation strategies on PrEP persistence among women at high-risk for HIV acquisition in South Africa: an interrupted time-series study	64
ABSTRACT	65
INTRODUCTION	67
METHODS.....	68
RESULTS	74
DISCUSSION	77
CONCLUSION.....	85
REFERENCES	101
CHAPTER 5: CONCLUSIONS.....	104
Synthesis of Results	104
Directions for Future Research.....	105
Public Health Impact.....	106
CURRICULUM VITAE.....	108

LIST OF TABLES

Chapter 2, Table 1. Hazard of PrEP discontinuation and sub-hazard ratios of two consecutive missed visits, client-initiated discontinuation, and provider-initiated discontinuation among 2776 female sex workers initiating PrEP through TB HIV Care in Durban, South Africa 2016-2020.....	24
Chapter 2, Appendix Table 1. Kaplan-Meier survivor function with time-to-event outcome defined as not being retained on PrEP among 2776 female sex workers initiating PrEP through TB HIV Care in Durban, South Africa 2016-2020.....	26
Chapter 3, Table 1. Characteristics of female sex workers (FSW) and adolescent girls and young women (AGYW) initiating PrEP through TB HIV Care between 2016 and 2021	52
Chapter 3, Table 2. Hazard of PrEP discontinuation among female sex workers and adolescent girls and young women initiating PrEP through TB HIV Care in South Africa 2016-2021	58
Chapter 3, Appendix Table 1. Kaplan-Meier estimates of discontinuation for 1-month, 4-month, and 7-month persistence on PrEP and cumulative incidence of re-initiation at 3-months, stratified by population (female sex workers and adolescent girls and young women) and site	60
Chapter 4, Table 1. Implementation strategies utilized by TB HIV Care to improve PrEP persistence and the specific sites that adopted strategies between June 2016 and August 2021	87
Chapter 4, Table 2. Model results from a primary analysis of the impact of several implementation strategies on the 1-month persistence among female sex workers initiating PrEP through TB HIV Care and three secondary analyses	91
Chapter 4, Appendix Table 1. Implementation Strategies designed to promote PrEP persistence implemented by TB HIV Care	92

Chapter 4, Appendix Table 2. Timing of TB HIV Care implementation strategy roll-out, availability of pre-strategy and post-strategy data, and decision about whether or not to include data in final interrupted time-series model	93
--	----

LIST OF FIGURES

Chapter 2, Figure 1. Number of PrEP eligible (HIV-negative and accessing services through TB HIV Care) and number and percentage of PrEP initiations each year among female sex workers in Durban, South Africa, 2016-2020	23
Chapter 2, Figure 2. Stacked cumulative incidence functions plotting the competing risks of those who remained on PrEP, those who did not return (two consecutive missed visits), client-initiated discontinuation, and provider-initiated discontinuation among 2776 female sex workers initiating PrEP through TB HIV Care in eThekweni, South Africa 2016-2020	25
Chapter 3, 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).....	53
Chapter 3, 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	54
Chapter 3, 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.....	55
Chapter 3, 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).....	56
Chapter 3, Figure 5. Persistence on PrEP at 1-month plotted against the number of initiations seen in the program by site among female sex workers and adolescent girls and young women between 2016 and 2021 at TB HIV Care	57
Chapter 3, Appendix Figure 1. Proportion initiating over time by site among female sex workers and adolescent girls and young women who were eligible for PrEP between 2016 and 2021 at TB HIV Care	59

Chapter 4, Figure 1. Map of South African provinces where TB HIV Care operates PrEP delivery programs for female sex workers (FSW) and adolescent girls and young women (AGYW), 2016-2021	86
Chapter 4, Figure 2. 1-month PrEP persistence (number persisting/total initiated in the prior month) over calendar time among female sex workers and adolescent girls and young women receiving PrEP from TB HIV Care	89
Chapter 4, Figure 3. Monthly trends in the 1-month PrEP persistence (number persisting/total initiated in the prior month) by site implementing PrEP as part of the TB HIV Care program for female sex workers visualized against the introduction of several implementation strategies designed to promote PrEP persistence.....	90
Chapter 4, Appendix Figure 1. Residuals plotted against predicted values from Poisson regression model examining implementation strategies among female sex workers ..	100

ABBREVIATIONS

AGYW	Adolescent Girls and Young Women
AIC	Akaike Information Criteria
BIC	Bayesian Information Criteria
CDC	Centers for Disease Control and Prevention
CHR	Cause-specific Hazard Ratio
COVID-19	Coronavirus disease of 2019
DREAMS	Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe Initiative
FEM-PrEP	Preexposure Prophylaxis Trial for HIV Prevention among African Women
FSW	Female Sex Workers
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
ITS	Interrupted Time Series
NGO	Non-Governmental Organization
NICD	National Institute of Communicable Diseases
PEPFAR	The United States President's Emergency Plan for AIDS Relief
PrEP	Pre-Exposure Prophylaxis for HIV Prevention
TB	Tuberculosis
RCT	Randomized Controlled Trial
SHR	Subdistribution-Hazard Ratio
SMS	Short Message Service
STIs	Sexually Transmitted Infections
TAPS	Treatment And Prevention for Female Sex Workers in South Africa
VOICE	The Vaginal and Oral Interventions to Control the Epidemic trial

CHAPTER 1: INTRODUCTION

HIV incidence in South Africa: young women at disproportionately high risk

Globally, 1.5 million people are newly infected each year with HIV.¹ 70% of these infections occur in just ten countries, and South Africa is home to close to one in seven.² This is the equivalent of 230,000 new persons living with HIV each year.² While the country saw substantial declines in incidence in the early and mid 2000s, largely due to advances in HIV testing and early prevention efforts, the current rate of new infections remains among the highest in the world.^{1,2}

Despite the incredibly high overall risk in the general population, young women are disproportionately affected by HIV in South Africa.³ Adolescent girls and young women, ages 15-24 years old represent less than 10% of the total population, yet make up close to 1 in 3 of all new infections.⁴⁻⁶ Young women in South Africa are approximately five times as likely to be living with HIV than their male counterparts and acquire HIV five to seven years earlier.⁴⁻⁶

Female sex workers, who share many of the same risks as adolescent girls and young women at high-risk, bear an even greater proportional burden, with approximately 60% nationally living with HIV.⁷⁻⁹ Although adolescent girls and young women and young female sex workers are often perceived as separate groups, data from across Southern and Eastern Africa highlight overlapping risk factors for HIV.^{5,10,11} Adolescent girls and young women engaged in transactional sex (sex in exchange for material support or other benefits, but not money) experience over two times the odds of HIV infection

compared to other adolescent girls and young women.^{5,10,11} Young women who engage in age-disparate relationships, have multiple partners, and/or have transactional sex may be considered more similar in terms of HIV risk to young female sex workers than to other lower risk adolescent girls and young women.^{5,10,11} Coupled with ongoing testing, scale-up of tools and strategies that address the unique prevention needs of young women at high-risk for HIV are needed.¹²

Pre-exposure prophylaxis for HIV prevention (PrEP) is an efficacious tool to prevent new HIV infections

PrEP has been shown to reduce HIV acquisition among women by close to 90% when taken daily.^{13,14} PrEP offers specific benefits to young women over existing HIV prevention methods. Young women at high-risk for HIV may face stigma and sexual or physical violence that may make it difficult to access and keep condoms on their person, or they may experience power imbalances in partnerships that challenge negotiation of condom use.¹⁵ PrEP is freely available and can be used autonomously without the consent or approval of a parent, partner, or client, creating an opportunity for women to protect themselves from HIV.^{16,17} In 2016, South Africa became one of the first countries in sub-Saharan African to offer PrEP as part of the national HIV program.^{18,19} The initial target population of PrEP roll-out was female sex workers, but as of 2018, PrEP provision had been expanded to include other groups at high-risk, including adolescent girls and young women.¹⁹ The World Health Organization has recommended that PrEP be offered to young women in high burden settings as part of HIV prevention packages.²⁰

Persistence and adherence challenges

Despite its proven efficacy, poor adherence can make PrEP essentially futile.²¹⁻²³ The effectiveness of PrEP is contingent on PrEP persistence and regular medication adherence, with greater protection conferred by more consistent pill-taking.^{14,22,24,25} Regular, daily use is particularly important for women compared with men, due to the greater amount of tenofovir disoproxil fumarate needed to create protective levels in vaginal tissues.^{26,27} Across both research and real-world settings, poor persistence and adherence have challenged the effective use of PrEP. The VOICE trial, which was a study of about 5000 reproductive aged women in South Africa, Uganda, and Zimbabwe, showed no reduction in new infections when comparing the oral PrEP arm with the placebo arm.²⁸ Investigators noted that this lack of effect was likely due to the very low levels of adherence seen in this study.²⁸ In a random sample of participants, tenofovir was detected in less than 30% of plasma samples.²⁸

Low levels of initiation and persistence among young women have also been seen in the South African National PrEP program. Early demonstration projects in South Africa, including the *TAPS* study²⁹ among 224 female sex workers in Johannesburg between 2015 and 2017 and *PlusPills*³⁰ among 148 adolescent girls and young women between 2015 and 2016 in Soweto and Cape Town, suggested that PrEP use declines to 50% 1-month after initiation and continues to decline further after that.^{29,30} Real-world data on PrEP initiation and persistence among South African young women at high-risk remain limited.

PrEP cycling

Unlike treatment for HIV, biomedical HIV prevention strategies like PrEP are not meant to be taken lifelong and instead are recommended when there is an elevated risk of HIV acquisition. Elevated risk of HIV may be episodic, coinciding with specific events, periods of risky activity, changes in partner dynamics, etc.³¹ As a result, it is expected to see some women cycling on and off PrEP intentionally based on changes in actual and perceived risk.³¹ Discontinuation of PrEP could indicate a real loss from prevention services or it could indicate an intentional discontinuation.³¹ While the current literature suggests a large proportion of women who initiate PrEP discontinue at 1-month,^{29,30} little is known about patterns of re-initiation and cycling over time.

Implementation strategies to improve PrEP use

There exist a number of identified barriers to PrEP, and these barriers can be grouped into patient-level, clinic-level, and community-level barriers. Patient-level barriers include limited awareness of PrEP, incongruent risk perception, and concerns over side effects.³²⁻³⁵ Clinic-level barriers include limited provider knowledge, overburdened staff and high case loads, and poor communication with patients.³⁵⁻³⁸ Community-level barriers include HIV-related stigma, stigma around premarital sex, limited access to PrEP outside of healthcare facilities, and lack of support from parents, partners, and community members who may influence patient decision-making.^{23,35,39} The obstacles to PrEP use are numerous and multi-factorial, and several implementation strategies have been developed to try and address these barriers.³⁵ These strategies, however, remain untested as they relate to PrEP and have largely been adapted from strategies that have

worked well to improve HIV treatment delivery.^{29,30,40,41} The delivery and use of PrEP are inherently different from that of HIV treatment and therefore there exists a need to evaluate the effectiveness of these strategies in the HIV prevention context.

TB HIV Care and the use of routinely collected data

For this dissertation, we have built on an existing research-practice partnership with TB HIV Care, the largest PrEP provider to young women in South Africa.^{9,42-47} TB HIV Care began a series of HIV prevention efforts, including HIV testing and counseling, sexually transmitted infection screening and treatment, and condom provision in 2012. In 2016, TB HIV Care began providing PrEP to female sex workers and expanded to include adolescent girls and young women in 2018. Sites offer HIV prevention services through mobile van health clinics and drop-in center wellness clinics. As of the submission of this dissertation (May 2022), TB HIV Care has initiated over 40,000 young women and female sex workers on PrEP.

As funding for HIV prevention continues to decline, creative ways to make efficient use of existing data are needed to inform evidence-based program delivery and decision-making.⁴⁸ In this dissertation, we used exclusively routine program data collected for the purposes of program management. Our goals in using these data were not only to understand PrEP delivery and answer program-relevant questions, but also to help improve and strengthen program systems along the way, including how data are captured, managed, and used.

REFERENCES

1. UNAIDS. Global HIV & AIDS statistics — Fact sheet. 2022.
<https://www.unaids.org/en/resources/fact-sheet>.
2. UNAIDS. South Africa. 2022.
<https://www.unaids.org/en/regionscountries/countries/southafrica>.
3. HIV prevention among adolescent girls and young women: Putting HIV prevention among adolescent girls and young women on the Fast-Track and engaging men and boys: UNAIDS, 2016.
4. Joint United Nations Programme on HIV/AIDS. Empower young women and adolescent girls: fast-tracking the end of the AIDS epidemic in Africa. Geneva: UNAIDS 2015.
5. Dellar RC, Dlamini S, Karim QA. Adolescent girls and young women: key populations for HIV epidemic control. *J Int AIDS Soc* 2015; **18**(2 Suppl 1): 19408.
6. Birdthistle I, Tanton C, Tomita A, et al. Recent levels and trends in HIV incidence rates among adolescent girls and young women in ten high-prevalence African countries: a systematic review and meta-analysis. *Lancet Glob Health* 2019; **7**(11): e1521-e40.
7. Baral S, Beyrer C, Muessig K, et al. Burden of HIV among female sex workers in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; **12**(7): 538-49.
8. Konstant TL, Rangasami J, Stacey MJ, Stewart ML, Nogoduka C. Estimating the number of sex workers in South Africa: rapid population size estimation. *AIDS Behav* 2015; **19 Suppl 1**: S3-15.
9. Schwartz S, Lambert A, Phaswana-Mafuya N, et al. Engagement in the HIV care cascade and barriers to antiretroviral therapy uptake among female sex workers in Port Elizabeth, South Africa: findings from a respondent-driven sampling study. *Sexually transmitted infections* 2016.
10. Kilburn K, Ranganathan M, Stoner MCD, et al. Transactional sex and incident HIV infection in a cohort of young women from rural South Africa. *AIDS* 2018; **32**(12): 1669-77.
11. Ranganathan M, Heise L, Pettifor A, et al. Transactional sex among young women in rural South Africa: prevalence, mediators and association with HIV infection. *J Int AIDS Soc* 2016; **19**(1): 20749.
12. Abdool Karim Q, Baxter C, Birx D. Prevention of HIV in Adolescent Girls and Young Women: Key to an AIDS-Free Generation. *J Acquir Immune Defic Syndr* 2017; **75 Suppl 1**: S17-S26.
13. Thomson KA, Baeten JM, Mugo NR, Bekker LG, Celum CL, Heffron R. Tenofovir-based oral preexposure prophylaxis prevents HIV infection among women. *Curr Opin HIV AIDS* 2016; **11**(1): 18-26.
14. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363**(27): 2587-99.

15. Duhaime-Ross A. There's a pill that prevents HIV — why are only gay men talking about it? *The Verge*. 2014.
16. Buchbinder SP. Maximizing the Benefits of HIV Preexposure Prophylaxis. *Top Antivir Med* 2018; **25**(4): 138-42.
17. Braksmajer A, Senn TE, McMahon J. The Potential of Pre-Exposure Prophylaxis for Women in Violent Relationships. *AIDS Patient Care STDS* 2016; **30**(6): 274-81.
18. Bekker LG, Rebe K, Venter F. Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection. *South African Journal of HIV Medicine* 2016; **17**(1).
19. NDoH. PrEP Implementation Pack: South Africa 2016-2016, 2016.
20. WHO. Guidelines on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. *World Health Organization* 2015.
21. van der Straten A, Stadler J, Montgomery E, et al. Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. *PLoS One* 2014; **9**(2): e89118.
22. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012; **367**(5): 411-22.
23. Mayer KH, Sullivan PS, Beyrer C. Silver bullets and structural impediments to HIV prevention. *Lancet HIV* 2019; **6**(11): e729-e32.
24. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367**(5): 399-410.
25. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2013; **381**(9883): 2083-90.
26. Hendrix CW. Exploring concentration response in HIV pre-exposure prophylaxis to optimize clinical care and trial design. *Cell* 2013; **155**(3): 515-8.
27. Cottrell ML, Yang KH, Prince HM, et al. A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine. *J Infect Dis* 2016; **214**(1): 55-64.
28. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015; **372**(6): 509-18.
29. Eakle R, Gomez GB, Naicker N, et al. HIV pre-exposure prophylaxis and early antiretroviral treatment among female sex workers in South Africa: Results from a prospective observational demonstration project. *PLoS Med* 2017; **14**(11): e1002444.
30. Gill K, Pidwell T, Dietrich J, et al. A Demonstration Open Label Study to Assess the Acceptability, Safety and Use of Truvada Pre-exposure Prophylaxis

in Healthy, HIV-Uninfected Adolescents, 15-19 Years of Age. Conference of the International AIDS Society. Paris, France; 2017.

31. Underhill K, Guthrie KM, Collieran C, Calabrese SK, Operario D, Mayer KH. Temporal Fluctuations in Behavior, Perceived HIV Risk, and Willingness to Use Pre-Exposure Prophylaxis (PrEP). *Arch Sex Behav* 2018; **47**(7): 2109-21.
32. Goparaju L, Experton LS, Praschan NC, Warren-Jeanpiere L, Young MA, Kassaye S. Women want Pre-Exposure Prophylaxis but are Advised Against it by Their HIV-positive Counterparts. *J AIDS Clin Res* 2015; **6**(11): 1-10.
33. Mack N, Odhiambo J, Wong CM, Agot K. Barriers and facilitators to pre-exposure prophylaxis (PrEP) eligibility screening and ongoing HIV testing among target populations in Bondo and Rarieda, Kenya: results of a consultation with community stakeholders. *BMC Health Serv Res* 2014; **14**: 231.
34. Eakle R, Bourne A, Jarrett C, Stadler J, Larson H. Motivations and barriers to uptake and use of female-initiated, biomedical HIV prevention products in sub-Saharan Africa: an adapted meta-ethnography. *BMC Public Health* 2017; **17**(1): 968.
35. Pinto RM, Berringer KR, Melendez R, Mmeje O. Improving PrEP Implementation Through Multilevel Interventions: A Synthesis of the Literature. *AIDS Behav* 2018; **22**(11): 3681-91.
36. Goparaju L, Praschan NC, Warren-Jeanpiere L, Experton LS, Young MA, Kassaye S. Stigma, Partners, Providers and Costs: Potential Barriers to PrEP Uptake among US Women. *J AIDS Clin Res* 2017; **8**(9).
37. Kambutse I, Igiraneza G, Ogbuagu O. Perceptions of HIV transmission and pre-exposure prophylaxis among health care workers and community members in Rwanda. *PLoS One* 2018; **13**(11): e0207650.
38. Pilgrim N, Jani N, Mathur S, et al. Provider perspectives on PrEP for adolescent girls and young women in Tanzania: The role of provider biases and quality of care. *PLoS One* 2018; **13**(4): e0196280.
39. Collier KL, Colarossi LG, Sanders K. Raising Awareness of Pre-Exposure Prophylaxis (PrEP) among Women in New York City: Community and Provider Perspectives. *J Health Commun* 2017; **22**(3): 183-9.
40. Machado DM, de Sant'Anna Carvalho AM, Riera R. Adolescent pre-exposure prophylaxis for HIV prevention: current perspectives. *Adolesc Health Med Ther* 2017; **8**: 137-48.
41. Gomez GB, Eakle R, Mbogua J, Akpomiemie G, Venter WD, Rees H. Treatment And Prevention for female Sex workers in South Africa: protocol for the TAPS Demonstration Project. *BMJ Open* 2016; **6**(9): e011595.
42. Comins C, Parmley L, Schwartz S, et al. Barriers and facilitators to successful decentralized treatment provision for female sex workers living with HIV in Durban, South Africa. International AIDS Conference. Amsterdam, The Netherlands; 2018.
43. Comins C, Schwartz S, Phetlhu DR, et al. Siyaphambili protocol: An evaluation of randomized, nurse-led adaptive HIV treatment interventions for

cisgender female sex workers living with HIV in Durban, South Africa. *Research in Nursing and Health* 2018; **In Press**.

44. Mishra S, Ma H, Schwartz S, et al. Epidemic impact of sustained viremia among female sex workers in South Africa. Conference on Retroviruses and Opportunistic Infections. Seattle, Washington; 2019.

45. Parmley L, Rao A, Kose Z, et al. Antenatal care presentation and engagement in the context of sex work: exploring barriers to care for sex worker mothers in South Africa. *Reprod Health* 2019; **16**(Suppl 1): 63.

46. Parmley L, Rao A, Young K, et al. Female Sex Workers' Experiences Selling Sex during Pregnancy and Post-Delivery in South Africa. *Stud Fam Plann* 2019; **50**(3): 201-17.

47. Wells C, Schwartz S, Phaswana-Mafuya N, et al. Characterizing the Patterns of HIV Disclosure to Clients Among South African Female Sex Workers in Port Elizabeth. *AIDS Behav* 2018; **22**(12): 3924-32.

48. Resource Tracking for HIV Prevention Research & Development Working Group. HIV Prevention Research & Development Investments: 2000-2016. 2017. http://www.hivresourcetracking.org/wp-content/uploads/2017/12/HIV_resourceTracking2016.pdf.

CHAPTER 2: Persistence on oral pre-exposure prophylaxis (PrEP) among female sex workers in eThekweni, South Africa, 2016-2020

Amrita Rao¹, Hlengiwe Mhlophe², Carly Comins¹, Katherine Young³, Mfezi Mcingana³, Catherine Lesko¹, Ntambue Mulumba², Stefan Baral¹, Harry Hausler³, Sheree Schwartz¹

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore USA

²TB HIV Care, Durban South Africa

³TB HIV Care, Cape Town South Africa

Corresponding Author: Amrita Rao, ScM

Email: arao24@jhu.edu

Tel. 617 780 8853

Address: 615 N. Wolfe St. E6534 Baltimore MD 21205

Short Title: PrEP persistence among female sex workers in South Africa

This work was [published](#) in PLOS ONE on March 15th, 2022.

ABSTRACT

Background:

Despite the established efficacy of PrEP to prevent HIV and the advantages of a user-controlled method, PrEP uptake and persistence by women in both trials and demonstration projects has been suboptimal. We utilized real-world data from an HIV service provider to describe persistence on oral PrEP among female sex workers (FSW) in eThekweni, South Africa.

Methods:

We examined time from PrEP initiation to discontinuation among all FSW initiating PrEP at TB HIV Care in eThekweni between 2016-2020. We used a discrete time-to-event data setup and stacked cumulative incidence function plots, displaying the competing risks of 1) not returning for PrEP, 2) client discontinuation, and 3) provider discontinuation. We calculated hazard ratios using complementary log-log regression and sub-hazard ratios using competing risks regression.

Results:

The number of initiations increased each year from 155 (9.3%, $n=155/1659$) in 2016 to 1224 (27.5%, $n=1224/4446$) in 2020. Persistence 1-month after initiation was 53% (95% CI: 51%-55%). Younger women were more likely to discontinue PrEP by not returning compared with those 25 years and older. Risk of discontinuation through non-return declined for those initiating in later years. Despite the COVID-19 pandemic, a greater number of initiations and sustained persistence were observed in 2020.

Conclusions:

Low levels of PrEP persistence were observed, consistent with data among underserved women elsewhere. Encouragingly, the proportion of women persisting increased over time, even as the number of women newly initiating PrEP and staff workload increased. Further research is needed to understand which implementation strategies the program may have enacted to facilitate these improvements and what further changes may be necessary.

KEYWORDS: HIV prevention; PrEP; Female sex workers; South Africa

INTRODUCTION

Nearly one million people are newly infected with HIV annually in South Africa, constituting about 15% of global incident infections.[1] Female sex workers (FSW) bear a disproportionate burden of disease in the country. Estimates suggest that 60% of cisgender FSW are living with HIV compared with 19% of other adults of reproductive age.[1-4] FSW experience high levels of violence from clients, non-paying partners, sex work managers, and others.[5-6] This coupled with arrest, economic necessity to accept unsafe work conditions, and other power imbalances often compromise their ability to negotiate consistent condom use.[7-9] Pre-exposure prophylaxis for HIV prevention (PrEP) is an efficacious and user-controlled option to prevent new HIV infections.[10, 11] Daily oral PrEP can be used autonomously and discreetly, without the need of partner or client involvement, and presents an opportunity for women to protect themselves from HIV.[12, 13]

Despite the HIV protection conferred by PrEP, with some estimates suggesting that daily use reduces acquisition by 79-85% among women[10, 11], PrEP persistence among FSW in trial settings and demonstration projects has been low.[14, 15] Even if freely available, many factors influence a woman's decision to initiate and continue taking PrEP, including knowledge, side-effects, and accessibility of PrEP, along with actual and perceived risk of HIV acquisition, and PrEP stigma and social influence.[16-19]

South Africa became the first country in Sub-Saharan Africa to implement PrEP as part of their national strategy for HIV prevention and began providing PrEP to FSW in 2016.[20] PrEP has been primarily delivered through specific programs, which have existing HIV services in place and established rapport with community groups. The objective of this analysis was to describe PrEP persistence among cisgender FSW accessing PrEP in real-world conditions in eThekweni, KwaZulu-Natal from 2016 to 2020.

METHODS

To describe PrEP persistence among FSW, we utilized data collected by TB HIV Care as part of routine service delivery. TB HIV Care is a South African non-profit organization that serves as the country's largest PrEP provider for young women and FSW and began providing PrEP to FSW in 2016. They now operate at multiple sites across five provinces and offer services through mobile van health clinics and drop-in center wellness clinics.

The study population for this analysis includes cisgender FSW assigned female sex at birth who initiated PrEP through TB HIV Care in eThekweni between September 1st, 2016, and December 31st, 2020. Women would have been eligible to begin PrEP through TB HIV Care if they were already accessing prevention services (e.g. testing for pregnancy, STIs, or HIV; family planning) through the program serving FSW and were HIV-negative.

Data for this study come from a site-level register that is maintained to track PrEP uptake and persistence over time and manage patient follow-up and scheduling. This register has individual-level data on the date of first PrEP initiation and the outcomes of subsequent monthly visits, including whether or not individuals stopped and restarted PrEP. We followed women from PrEP initiation to discontinuation or administrative censoring at 12 months or December 2020, whichever came first. Discontinuation was defined as a composite outcome based on 1) not attending two consecutive visits (not returning for PrEP), 2) attending a monthly appointment and the client choosing to discontinue PrEP (client discontinuation), or 3) attending a monthly appointment and the clinician deciding to discontinue PrEP (provider discontinuation). Two consecutive missed visits was used to define discontinuation in alignment with TB HIV Care's PEPFAR reporting definition for loss to follow-up. If a client misses one visit, but returns the next month, the program notes this client as not attending a visit but continuing on PrEP. If a client misses two consecutive visits and returns subsequently, the program defines her as a "restart."

We examined time-to-PrEP discontinuation using a discrete time-to-event data setup, with person-periods defined for each month in which a woman was observed. We refer to the complement of PrEP discontinuation (i.e. 'survival' from discontinuation) as PrEP persistence. We plotted stacked cumulative incidence functions to show the differential risk of types of PrEP discontinuation (client discontinuation, provider discontinuation, not returning for PrEP) over time. We stratified analyses by age and era-of-initiation, defined as the year in which a woman initiated PrEP (2016-2020). We calculated

overall, “cause-specific” hazard ratios (CHR) for discontinuation by age and year of initiation using a complementary log-log regression model. We calculated subdistribution-hazard ratios (SHR) for each specific type of PrEP discontinuation using Fine and Gray survival models.[21] Results were determined to be statistically significant if the 95% confidence interval around the hazard ratio did not overlap with the line of no difference, which is 1 in the case of ratio measures. All analyses were conducted using Stata 14.2 (StataCorp, College Park, Texas, USA).

RESULTS

There were a total of 2776 FSW newly initiating PrEP at TB HIV Care in eThekweni between 2016 and 2020 and included in these analyses. Approximately 60% were women ages 25 years and older (1662/2762). The absolute number of PrEP initiations increased over time, and the percentage of PrEP initiations among those who were seen by the program and HIV-negative increased substantially in 2019 and 2020: 155/1659 (9.3%) in 2016, 211/3235 (6.5%) in 2017, 428/6042 (7.1%) in 2018, 756/5789 (13.1%) in 2019, and 1224/4446 (27.5%) in 2020 (**Chapter 2, Figure 1**). Based on the Kaplan-Meier survival function, PrEP persistence was 53% (95% CI: 51%-55%) 1-month after initiation, 33% (95% CI: 31%-35%) 4-months after initiation, and 18% (95% CI: 16%-19%) 7-months after initiation. By 12-months, 9% (95% CI: 7%-10%) persisted on PrEP. Details of the Kaplan-Meier survivor function are provided in the **Chapter 2, Appendix Table 1**. Among those who discontinued (n=2210), 13% restarted during the observation period (287/2210), with a median time from discontinuation to restart of 3 months (IQR: 3-5)

At 1-month after initiation, 56% (95% CI: 54%-59%) of women ≥ 25 years old persisted on PrEP compared with 48% (95% CI: 45%-51%) of women < 25 years old. The higher PrEP persistence seen in women ≥ 25 years was predominantly due to better attendance at follow-up visits compared with women < 25 years (SHR for program-defined loss to follow-up: 0.82, 95% CI: [0.76, 0.88]). There were no significant differences by age in client-initiated or provider-initiated discontinuation (**Chapter 2, Table 1**).

PrEP persistence improved over the course of the program (**Chapter 2, Figure 2**). In 2019, 62% of women persisted on PrEP 1-month after initiation (95% CI: 58%-65%). By comparison, in 2016, 52% of women persisted on PrEP 1-month after initiation (95% CI: 43%-59%). Women initiating PrEP in 2018 (SHR: 0.84, 95% CI: [0.72, 0.99]), 2019 (SHR: 0.64, 95% CI: [0.55, 0.75]) and 2020 (SHR: 0.82, 95% CI: [0.71, 0.95]) were statistically significantly less likely to stop coming back for their PrEP compared to those initiating in 2016, when accounting for the competing risks of client-initiated and provider-initiated discontinuation. Interestingly, there was a statistically significantly greater risk of client-initiated discontinuation in 2019 compared with 2016, with 150 client-initiated discontinuations out of the 756 who initiated in 2019, or 19.8%, (SHR: 3.41, 95% CI: [1.75, 6.63]) (**Chapter 2, Table 1**).

DISCUSSION

Among FSW accessing HIV prevention services from a real-world service provider in eThekweni, South Africa, the number of PrEP initiations increased each year from 2016

to 2020. PrEP persistence declined to 53% one month after initiation and to just 9% after one year. Younger women were more likely to discontinue PrEP due to missed visits compared with those 25 years and older. Risk of discontinuation due to missed visits declined for those initiating in 2018, 2019, and 2020, suggesting improvements over the life of the program in helping women to stay engaged. Despite the disruptions to the healthcare infrastructure created by the COVID-19 pandemic, the program reported more initiations, sustained improvements in persistence, and a lower risk of client-initiated stops among those initiating in 2020.

Poor PrEP persistence may challenge its real-world utility. The low levels of persistence seen in this study and the sharp decline at one-month are consistent with what has been reported in trials, including the FEM-PrEP study[22] and VOICE .[23] The *TAPS* demonstration study with FSW in South Africa also indicated that PrEP use declines to 50% one month after initiation and continues to decline after that.[14] The real-world data presented here reinforce the need for effective implementation strategies to improve PrEP persistence.

Losses were highest among those under 25 years, which is also the group of FSW at the highest risk of HIV acquisition. Nearly 30% of all new infections in South Africa are among young women and by age 25, 70% of FSW have been infected with HIV.[24] Younger women tend to have lower levels of HIV-related knowledge and lower risk perception.[25] Additionally, younger FSW may face specific challenges associated with their youth: less experience in the industry, less social support and fewer network ties,

greater vulnerability to violence, lack of financial autonomy, and underdeveloped self-efficacy.[26, 27] Strategies to promote PrEP persistence may need to be tailored to the specific challenges and needs of youth.

Over the life of the program, a number of changes have been implemented, both in terms of the goals of the program and the strategies implemented to try to achieve these goals. At the outset of the program, the primary goal was to try to promote PrEP uptake. As the program evolved, PrEP persistence grew to be a more central concern, with CDC/PEPFAR adding current users of PrEP as an official program target in 2019. The shifting priorities of the program may help explain the greater focus given to persistence and the observed improvements over time. Additionally, the program instituted several implementation strategies that aimed to address different barriers to PrEP persistence. The program added staff in June 2019 that included case managers and social workers. These additional staff meant more dedicated resources and greater flexibility to manage new PrEP users. The expanded use of the case management approach allowed for staff to call those who may have missed appointments. This closer follow-up may also help explain the reason for the increased risk of client-initiated discontinuation in 2019, as staff were actually able to ascertain and record that a woman no longer wanted to be on PrEP.

The data presented here show that the program was largely resilient to the interruptions caused by COVID-19, with a consistent increase in the number of initiations and improved persistence among those who began PrEP in 2020. Though empiric data on

the impact of COVID-19 on HIV services in Sub-Saharan Africa are limited, most suggest that patient care was interrupted by pandemic restrictions due to lower supply of drugs and fewer patient visits.[28-30] In a national survey in South Africa that recruited approximately 19,000 individuals via social media, it was found that 13.2% were unable to pick up their medications during the pandemic.[29] The implementation strategies started by the program coupled with the fact that HIV prevention and treatment services remained “essential” in South Africa during the COVID-19 pandemic may have made the program more resilient to the shocks of the pandemic.

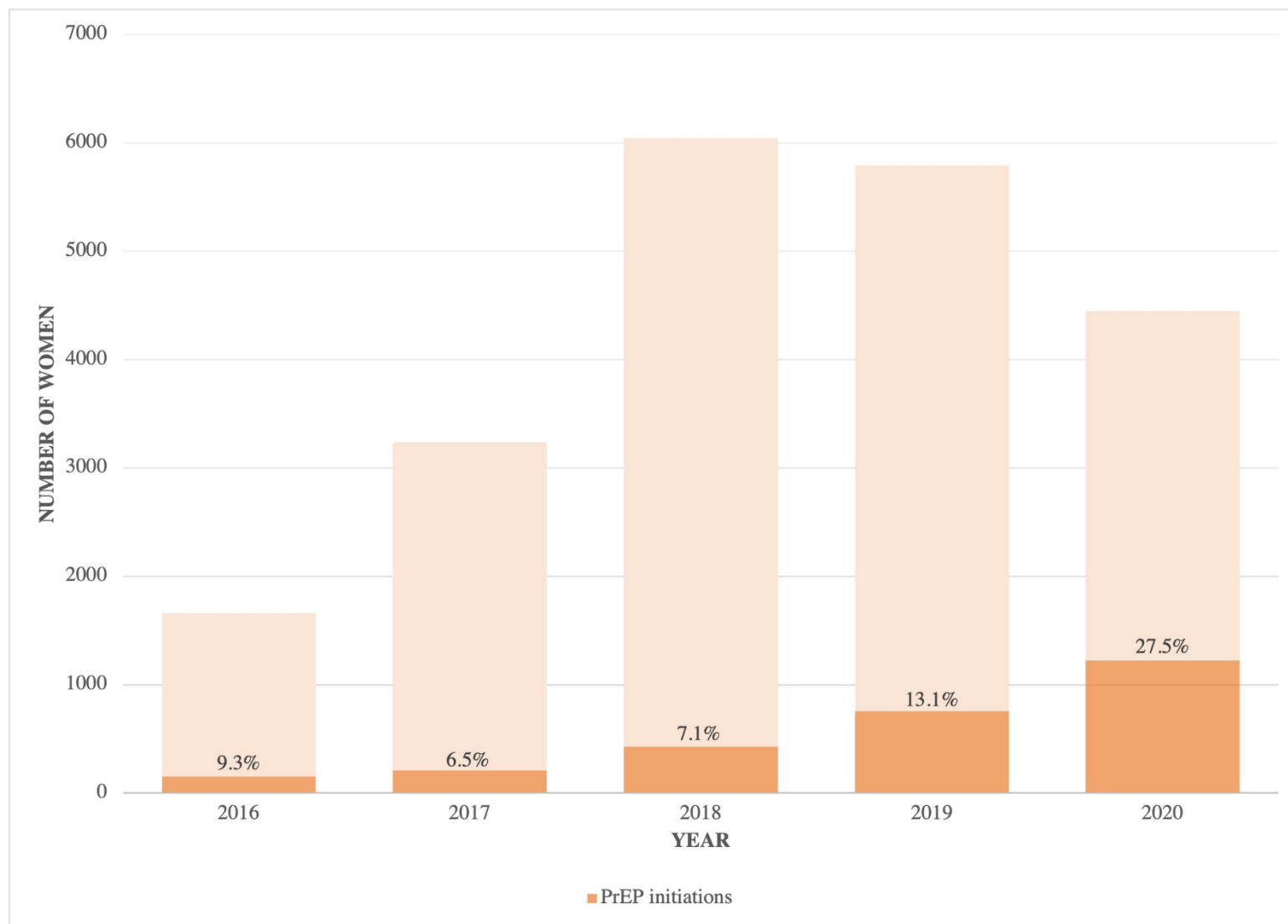
There are three key limitations of this study. First, the primary outcome in this study is PrEP persistence rather than adherence, which may be better captured through pill counts, electronic monitoring, or pharmacological samples, and arguably is an important measure of whether a woman was protected from acquiring HIV. PrEP persistence is probably a highly specific but not perfectly sensitive measure of PrEP adherence. PrEP was not available from other sources in the study setting during the study period (not persisting on PrEP is a good marker of not adhering to PrEP). Contrariwise, it is unlikely that women would return to pick up PrEP if they did not intend to take it (PrEP persistence is not a guarantee of PrEP adherence, but it is probably a reasonable proxy). If anything, we have overestimated PrEP adherence and our central conclusion (PrEP adherence is too low) is unchanged. A second limitation is that the frequency of PrEP refill visits changed during the study period. At the start of the program, women were seen monthly to be given their PrEP. When the guidelines were updated to allow for multi-month dispensing, women were seen at 1-month and thereafter 3-monthly (e.g.

1-month, 4-months, 7-months, etc.) to be given their PrEP. In many instances, however, the program did see the client in the intervening months between PrEP refill visits and would document whether an individual was still taking PrEP. While in later years this might have limited our ability to detect PrEP discontinuation with the same speed (e.g., discontinuation that occurred at month 2 might not be detected until month 4,) we chose to retain the definition of two missed monthly visits for discontinuation both to ensure comparability across the years and because the program's register still documents monthly contact with PrEP users. All discontinuations would still be detected within the outcome window (1 year) overall estimates of PrEP persistence at 4- and 7-months should not be affected. As a final limitation, because of limited data availability, demographic and/or behavioral risk data beyond age and year of PrEP initiation were not available to thoroughly assess predictors of persistence. Understanding who is at risk of discontinuation and reasons for discontinuation will be an important contribution to better tailoring strategies to promote PrEP persistence.

The need for PrEP, unlike treatment for HIV, depends heavily on individual risk-assessment and readiness. Some of the improved persistence over time could be explained by program staff better refining who they started on PrEP, that is, better identifying women who were in need of and who understood the benefit of taking PrEP or may in part be due to the role of diffusion of information (increasing PrEP awareness and awareness of the program) and greater acceptability among peers, partners, and others in the community. While this study describes how the program was able to make gradual improvements in PrEP persistence over time while reaching a larger number

and proportion of FSW over time, further research on which implementation strategies may have spurred some of these incremental changes and the mechanism of action are critical to see the additional gains in persistence that are needed.

Chapter 2, Figure 1. Number of PrEP eligible (HIV-negative and accessing services through TB HIV Care) and number and percentage of PrEP initiations each year among female sex workers in Durban, South Africa, 2016-2020

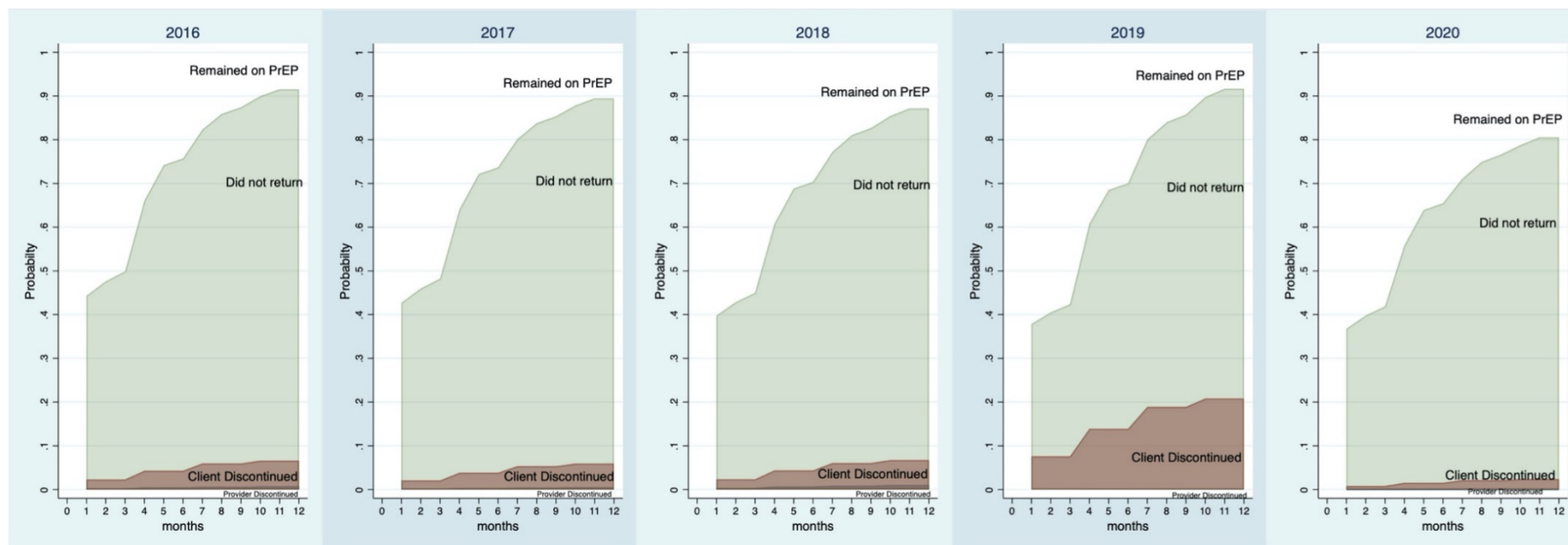


Chapter 2, Table 1. Hazard of PrEP discontinuation and sub-hazard ratios of two consecutive missed visits, client-initiated discontinuation, and provider-initiated discontinuation among 2776 female sex workers initiating PrEP through TB HIV Care in Durban, South Africa 2016-2020

UNIVARIABLE					
	Number of initiations	Discontinuation (composite outcome)	Two consecutive missed visits (n=1986)	Client-initiated discontinuation (n=217)	Provider-initiated discontinuation (n=7)
		Hazard ratio (95% CI)	Sub-hazard ratio (95% CI)		
Age¹					
<25 years old	1102	ref	ref	ref	ref
25+ years old	1662	0.80 (0.74, 0.86)	0.84 (0.79, 0.91)	0.97 (0.74, 1.26)	0.91 (0.20, 4.10)
Year²					
2016	155	ref	ref	ref	ref
2017	211	0.99 (0.82, 1.19)	0.96 (0.80, 1.16)	0.89 (0.37, 2.14)	0.73 (0.05, 11.72)
2018	428	0.84 (0.71, 1.00)	0.86 (0.73, 1.01)	1.02 (0.48, 2.16)	1.41 (0.16, 12.56)
2019	756	0.88 (0.75, 1.03)	0.67 (0.57, 0.78)	3.41 (1.75, 6.63)	0.20 (0.01, 3.09)
2020	1224	0.82 (0.70, 0.96)	0.83 (0.71, 0.96)	0.35 (0.16, 0.77)	<i>Too few events</i>
INCLUDING BOTH AGE AND YEAR IN THE SAME MODEL					
		Hazard ratio (95% CI)	Sub-hazard ratio (95% CI)		
Age¹					
<25 years old	1102	ref	ref	ref	ref
25+ years old	1662	0.80 (0.74, 0.86)	0.82 (0.76, 0.88)	1.10 (0.85, 1.43)	0.85 (0.18, 3.98)
Year²					
2016	155	Ref	ref	ref	ref
2017	211	0.96 (0.80, 1.16)	0.94 (0.78, 1.12)	0.90 (0.38, 2.16)	0.72 (0.04, 11.67)
2018	428	0.83 (0.70, 0.98)	0.84 (0.72, 0.99)	1.02 (0.48, 2.17)	1.40 (0.15, 13.10)
2019	756	0.85 (0.72, 0.99)	0.64 (0.55, 0.75)	3.46 (1.78, 6.71)	0.19 (0.01, 3.47)
2020	1224	0.82 (0.70, 0.96)	0.82 (0.71, 0.95)	0.36 (0.16, 0.78)	<i>Too few events</i>

¹Age data missing for n=12 (0.4%); ²Year of initiation data missing for n=2 (0.07%)

Chapter 2, Figure 2. Stacked cumulative incidence functions plotting the competing risks of those who remained on PrEP, those who did not return (two consecutive missed visits), client-initiated discontinuation, and provider-initiated discontinuation among 2776 female sex workers initiating PrEP through TB HIV Care in eThekweni, South Africa 2016-2020



Chapter 2, Appendix Table 1. Kaplan-Meier survivor function with time-to-event outcome defined as not being retained on PrEP among 2776 female sex workers initiating PrEP through TB HIV Care in Durban, South Africa 2016-2020

Month	At risk	Not retained ⁺	Net lost [§]	Survivor function	95% Confidence Interval
1	2776	1299	0	0.53	0.51-0.55
2	1476	73	90	0.51	0.49-0.52
3	1313	47	178	0.49	0.47-0.51
4	1088	346	39	0.33	0.31-0.35
5	703	154	42	0.26	0.24-0.28
6	507	25	38	0.25	0.23-0.26
7	444	126	41	0.18	0.16-0.19
8	277	53	2	0.14	0.13-0.16
9	222	22	5	0.13	0.11-0.14
10	195	42	1	0.10	0.09-0.12
11	152	23	3	0.09	0.07-0.10
12	126	0	126	0.09	0.07-0.10

⁺Not retained= did not return, client discontinued, provider discontinued

[§]Net lost=Lost from follow-up with no outcome determined. No late entries.

REFERENCES

1. UNAIDS South Africa.: UNAIDS, 2021.
2. Konstant TL, Rangasami J, Stacey MJ, Stewart ML, Nogoduka C. Estimating the number of sex workers in South Africa: rapid population size estimation. *AIDS Behav* 2015; **19 Suppl 1**: S3-15.
3. Schwartz S, Lambert A, Phaswana-Mafuya N, et al. Engagement in the HIV care cascade and barriers to antiretroviral therapy uptake among female sex workers in Port Elizabeth, South Africa: findings from a respondent-driven sampling study. *Sex Transm Infect* 2017; **93**(4): 290-6.
4. Grasso MA, Manyuchi AE, Sibanyoni M, et al. Estimating the Population Size of Female Sex Workers in Three South African Cities: Results and Recommendations From the 2013-2014 South Africa Health Monitoring Survey and Stakeholder Consensus. *JMIR Public Health Surveill* 2018; **4**(3): e10188.
5. Baral S, Beyrer C, Muessig K, et al. Burden of HIV among female sex workers in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; **12**(7): 538-49.
6. Beyrer C, Crago AL, Bekker LG, et al. An action agenda for HIV and sex workers. *Lancet* 2015; **385**(9964): 287-301.
7. Wirtz AL, Schwartz S, Ketende S, et al. Sexual violence, condom negotiation, and condom use in the context of sex work: results from two west african countries. *J Acquir Immune Defic Syndr* 2015; **68 Suppl 2**: S171-9.
8. Becker ML, Bhattacharjee P, Blanchard JF, et al. Vulnerabilities at First Sex and Their Association With Lifetime Gender-Based Violence and HIV Prevalence Among Adolescent Girls and Young Women Engaged in Sex Work, Transactional Sex, and Casual Sex in Kenya. *J Acquir Immune Defic Syndr* 2018; **79**(3): 296-304.
9. Jewkes RK, Dunkle K, Nduna M, Shai N. Intimate partner violence, relationship power inequity, and incidence of HIV infection in young women in South Africa: a cohort study. *Lancet* 2010; **376**(9734): 41-8.
10. Thomson KA, Baeten JM, Mugo NR, Bekker LG, Celum CL, Heffron R. Tenofovir-based oral preexposure prophylaxis prevents HIV infection among women. *Curr Opin HIV AIDS* 2016; **11**(1): 18-26.
11. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363**(27): 2587-99.
12. Buchbinder SP. Maximizing the Benefits of HIV Preexposure Prophylaxis. *Top Antivir Med* 2018; **25**(4): 138-42.
13. Braksmajer A, Senn TE, McMahon J. The Potential of Pre-Exposure Prophylaxis for Women in Violent Relationships. *AIDS Patient Care STDS* 2016; **30**(6): 274-81.
14. Eakle R, Gomez GB, Naicker N, et al. HIV pre-exposure prophylaxis and early antiretroviral treatment among female sex workers in South Africa: Results

from a prospective observational demonstration project. *PLoS Med* 2017; **14**(11): e1002444.

15. Gill K, Pidwell T, Dietrich J, et al. A Demonstration Open Label Study to Assess the Acceptability, Safety and Use of Truvada Pre-exposure Prophylaxis in Healthy, HIV-Uninfected Adolescents, 15-19 Years of Age. Conference of the International AIDS Society. Paris, France; 2017.

16. Pinto RM, Berringer KR, Melendez R, Mmeje O. Improving PrEP Implementation Through Multilevel Interventions: A Synthesis of the Literature. *AIDS Behav* 2018; **22**(11): 3681-91.

17. Eakle R, Bourne A, Jarrett C, Stadler J, Larson H. Motivations and barriers to uptake and use of female-initiated, biomedical HIV prevention products in sub-Saharan Africa: an adapted meta-ethnography. *BMC Public Health* 2017; **17**(1): 968.

18. Mack N, Odhiambo J, Wong CM, Agot K. Barriers and facilitators to pre-exposure prophylaxis (PrEP) eligibility screening and ongoing HIV testing among target populations in Bondo and Rarieda, Kenya: results of a consultation with community stakeholders. *BMC Health Serv Res* 2014; **14**: 231.

19. Goparaju L, Experton LS, Praschan NC, Warren-Jeanpiere L, Young MA, Kassaye S. Women want Pre-Exposure Prophylaxis but are Advised Against it by Their HIV-positive Counterparts. *J AIDS Clin Res* 2015; **6**(11): 1-10.

20. Bhavaraju N, Uribe D. PrEP Watch: Early Lessons from South Africa's Rollout of Oral PrEP to Sex Workers. <https://www.prepwatch.org/early-lessons-south-africa-rollout/>.

21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1997; **94**(446): 496-509.

22. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012; **367**(5): 411-22.

23. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015; **372**(6): 509-18.

24. Rucinski KB, Schwartz SR, Mishra S, et al. High HIV Prevalence and Low HIV-Service Engagement Among Young Women Who Sell Sex: A Pooled Analysis Across 9 Sub-Saharan African Countries. *J Acquir Immune Defic Syndr* 2020; **85**(2): 148-55.

25. Yang F, Li Z, Subramanian SV, Lu C. Assessment of Knowledge of HIV/AIDS and Association With Socioeconomic Disparities Among Young Women in Low- and Middle-Income Countries, 2003 to 2018. *JAMA Netw Open* 2021; **4**(1): e2035000.

26. Napierala S, Chabata ST, Fearon E, et al. Engagement in HIV Care Among Young Female Sex Workers in Zimbabwe. *J Acquir Immune Defic Syndr* 2018; **79**(3): 358-66.

27. Bowring AL, Ketende S, Rao A, et al. Characterising unmet HIV prevention and treatment needs among young female sex workers and young men who have sex with men in Cameroon: a cross-sectional analysis. *Lancet Child Adolesc Health* 2019; **3**(7): 482-91.
28. Nachega JB, Kapata N, Sam-Agudu NA, et al. Minimizing the impact of the triple burden of COVID-19, tuberculosis and HIV on health services in sub-Saharan Africa. *Int J Infect Dis* 2021.
29. Jewell BL, Mudimu E, Stover J, et al. Potential effects of disruption to HIV programmes in sub-Saharan Africa caused by COVID-19: results from multiple mathematical models. *Lancet HIV* 2020; **7**(9): e629-e40.
30. Shiao S, Krause KD, Valera P, Swaminathan S, Halkitis PN. The Burden of COVID-19 in People Living with HIV: A Syndemic Perspective. *AIDS Behav* 2020; **24**(8): 2244-9.

CHAPTER 3: Longitudinal patterns of initiation, persistence, and cycling on PrEP among female sex workers and adolescent girls and young women across multiple program sites in South Africa, 2016-2021

Amrita Rao¹, Catherine Lesko¹, Hlengiwe Mhlophe², Katherine Rucinski³, Mfezi Mcingana², Anje Pretorius², Jennifer Mcloughlin², Stefan Baral¹, Harry Hausler², Sheree Schwartz¹

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore USA

²TB HIV Care, Cape Town South Africa

³Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore USA

Corresponding Author: Amrita Rao, ScM

Email: arao24@jhu.edu

Tel. 617 780 8853

Address: 615 N. Wolfe St. E6534 Baltimore MD 21205

ABSTRACT

Background

Young women, including female sex workers (FSW) and adolescent girls and young women (AGYW), face a disproportionately high risk of HIV acquisition in South Africa, accounting for almost a third of new infections in the country. Oral PrEP has the potential to avert some of these new infections, but its effectiveness is highly linked to consistent use. Early discontinuation of PrEP in this population is high, but less is known about the longitudinal patterns of PrEP use, including patterns of re-initiation and cycling.

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 in these analyses. Using survival analyses and group-based trajectory modeling, we described patterns of initiation, first discontinuation, re-initiation, and cycling.

Results

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 (i.e., restarting after missing two consecutive months of PrEP), however less than 10% of FSW 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). We did not identify a group for either population that was consistently using PrEP. The greater the number of initiations in a given month, the poorer the persistence among AGYW, but there was no observed relationship between initiations and persistence among FSW.

Conclusions

Persistence on PrEP was shown to be 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 increasingly factor in PrEP readiness and persistence support, to achieve public health impact

INTRODUCTION

HIV incidence is disproportionately high among adolescent girls and young women (AGYW) 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 its 230,000 new infections annually.^{1,2} Compared with their male counterparts, young women in South Africa are more likely to be infected with HIV, and infection occurs approximately five to seven years earlier.³⁻⁷ As many as 60% of FSW, who make a majority of their income selling sex, are estimated to be living with HIV. The incidence rate in younger FSW is approximately 13.2 per 100 person years.⁶ While AGYW and FSW are often treated as separate groups by HIV prevention programs, they share many risk factors for HIV acquisition, including age-disparate relationships, difficulty negotiating condom use, and economic instability.^{5,8-10} Little progress has been made toward mitigating their risk, despite the significant need.²

Oral pre-exposure prophylaxis (PrEP) has emerged as an HIV prevention tool that is ~90% efficacious at preventing new HIV infection when used consistently.¹¹⁻¹³ Because it can be accessed without the need for consent or approval of their parents or partners as early as age 15, it is prevention tool that is promising for addressing some of the unique structural HIV prevention challenges facing AGYW and FSW. But early discontinuation and inconsistent pill-taking undermine the effective use of PrEP.¹⁴ In prior demonstration studies in South Africa, approximately half of women discontinued PrEP by 1-month followed by further declines in use.^{15,16} However, there is as yet no

longitudinal data on PrEP use among AGYW and FSW who initiate and discontinue PrEP at least once.

The need for PrEP, unlike the need for HIV treatment, can differ not only between individuals, but also within individuals over time.¹⁷ Risk of HIV may be episodic, related to specific events or periods of risky activity. Individuals may cycle on and off PrEP coinciding with changes to their perceived risk of HIV, sometimes referred to as risk-use alignment.¹⁷⁻¹⁹ Among women who initiate PrEP in South Africa, patterns of use following discontinuation are not well understood, but are important in terms of program implementation and management, decisions about who should be initiated on PrEP, and concerns about potential future resistance to antiretrovirals.¹⁷

Further, because PrEP in South Africa is largely delivered through implementing partners with finite time, resources, and staff, increasing program sizes and more people receiving PrEP may mean fewer resources to support PrEP persistence. To add to this, emphasis on initiating more women with varying risk for HIV may mean that those initiating during these pushes to initiate are less likely to remain persistent relative to those who took up PrEP when services first became available. 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 discontinuation, re-initiation, and cycling among FSW and AGYW who initiated PrEP through TB HIV Care,

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

METHODS

Study Population and Setting

TB HIV Care is a South African NGO that provides a range of TB, HIV, and other health services to populations at high risk, including FSW and AGYW. TB HIV Care serves as the largest PrEP provider to young women in the country. Data for this analysis come from routinely collected, site-level or clinic-level registers that track PrEP use over time. Sites roughly correspond to the district unit of administration; clinics refer to specific health facilities from which TB HIV Care operates. Women in this study were categorized as AGYW or FSW according to the program through which they were recruited and from which they received services. TB HIV Care generally recruits and provides services to FSW from known sex work venues (e.g. brothels, bars, street-based venues) and AGYW from locations where young women tend to congregate and are likely to be found (e.g. schools, community centers, and areas of commerce). AGYW are eligible to receive services from TB HIV Care if they weigh at least 35 kilograms.

FSW were served by nine sites in five provinces: 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 on paper forms and stores these forms in locked and secure file cabinets in the local program offices. Data capturers then enter these data into population-specific registers once a week for each site.

We included FSW and AGYW who accessed health services from TB HIV Care (e.g. HIV testing, sexual and reproductive health services) and who tested negative for HIV and were therefore eligible for PrEP. We included those women who were engaged with TB HIV Care from when PrEP was first made available to each population 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, because the format of the AGYW PrEP registers changed in October 2020 and data were no longer compatible with the present analyses.

Outcomes

The primary outcomes of interest included PrEP initiation, discontinuation, and re-initiation. PrEP initiation was defined as choosing to start on oral pre-exposure prophylaxis (tenofovir/emtricitabine) and taking home a 1-month supply of pills through TB HIV Care. 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. For women who

regularly use TB HIV Care services, HIV testing is recommended every three months, although women may test more or less frequently. Among women who initiated PrEP, we defined discontinuation as two consecutive missed PrEP visits, a client-initiated stop, or a provider-initiated stop. PrEP visits were scheduled to occur monthly after initiation. This definition of PrEP discontinuation is the one used by the program in alignment with PEPFAR reporting definitions.²⁰ Re-initiation was defined as restarting PrEP within 12 months of an initial PrEP prescription, after a ≥ 2 month gap in PrEP (a discontinuation).

Covariates

We also assessed woman's age (categorical variable: 18 years old or younger, 19-24 years old, 25-34 years old, and 35 years old or older) and year of PrEP initiation (2016-2021) as potential covariates of PrEP discontinuation.

Statistical analyses

We estimated the proportion of eligible women who initiated PrEP as a function of calendar time, persistence on PrEP as a function of time since PrEP initiation, and re-initiation on PrEP as a function of time since PrEP discontinuation. We attempted to describe cycling on and off by characterizing subgroups of women according to their trajectories of PrEP use.

We also described correlates of PrEP persistence, including age and year of initiation, and modeled the 1-month persistence on PrEP as a function of the total number of

women initiated on PrEP across calendar time (to examine the hypothesis that persistence decreases with a greater number of initiations, potentially because of 1) fewer resources per woman available to dedicate to persistence and 2) changing risk-level with a growing program and that when more women initiated PrEP the average risk went down).

Initiation

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

Discontinuation

We examined the time from PrEP initiation to first discontinuation using Kaplan-Meier survival curves, overall by population and stratified by site. Individuals were censored after 12 months of follow-up 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 some of the burden on women 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. For the purposes of these analyses, 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.²⁰

Re-initiation

To explore patterns of re-initiation, we estimated time from PrEP discontinuation to re-initiation using the complement of Kaplan-Meier survival curves to estimate cumulative incidence of re-initiation, overall 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 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.” Individuals could cycle on and off PrEP throughout the duration of follow-up. We considered constant, 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 and adherence in the literature.^{21,22}

Correlates of discontinuation

To better understand patterns of discontinuation over time, we described correlates of discontinuation using available data. First, we plotted 1-month persistence (defined as those still retained at one month among those who initiated PrEP) against the total number of initiations in a given month, stratifying by population and site. 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 stratified by site, age, and year of initiation using a 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 TB HIV Care during the study period and were included in these analyses, including 12,581 FSW between June 2016 and August 2021 and 28,100 AGYW between May 2018 and September 2020. Among FSW, the two largest sites were eThekweni (n=3,268, 26% of all FSW) and uMgungundlovu

(n=2,919, 23%), and the smallest site was Ngaka Modiri Molema (n=226, 2%). Among AGYW, the two largest sites were Cape Town (n=9,660, 34% of all AGYW) and uMgungundlovu (n=11,866, 43%), and the smallest was eThekweni (n=2,890, 10%). Over one third of AGYW were adolescents (18 years old or younger). A large proportion of both populations was between the ages of 19 and 34 years old: more than 3 out of 4 FSW (n=9885, 79%) and more than half of AGYW (n=17,142, 61%) (**Chapter 3, Table 1**).

Initiation

The number of initiations increased for both the FSW and AGYW programs, 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 (**Chapter 3, Table 1**). Across the study period, approximately 19% (12,581/65,782) of negative test encounters resulted in a PrEP 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 (**Chapter 3, Figure 1**). At sites that began providing PrEP later in calendar time, in general, the proportion of eligible FSW who initiated PrEP was higher to start, and there was not a clear increasing trend in PrEP initiations (**Chapter 3, Appendix Figure 1**). Among AGYW overall, there was no clear trend in the proportion initiating over time, though it appears to have increased slightly (**Chapter 3, Figure 1**). There was also substantial heterogeneity in PrEP use across sites. At the two largest sites, there was a clear increase in initiations over time, while at one smaller site there was a dramatic decrease. Further, one site only

contributed 4 months of observations due to missing data (**Chapter 3, Appendix Figure 1**).

Discontinuation

The 40,681 individuals who initiated PrEP during this period contributed 90,377 person-months to the analysis of time to discontinuation. Both FSW and AGYW had low persistence on PrEP, with 41% (95% CI: 40%-42%) of FSW and 38% (95% CI: 37%-38%) persisting at 1-month (**Chapter 3, Figure 2**). Over the 12 months of follow-up, AGYW experienced a slightly earlier drop-off in PrEP persistence (**Chapter 3, Figure 2**). PrEP persistence for AGYW was 38% (95% CI: 37%-38%) at 1 month, 13% (95% CI: 13%-13%) at 4 months, and 5% (95% CI: 5%-6%) at 7 months. For FSW, 1-month persistence was 41% (95% CI: 40%-42%), 4-month persistence was 18% (95% CI: 18%-19%), and 7-month persistence was 7% (7%-86%) (**Chapter 3, Appendix Table 1**). There was substantial heterogeneity across sites (**Chapter 3, Figure 2**), particularly for AGYW. Among AGYW, the 1-month persistence for eThekweni and uMgungundlovu was 63% (61%-65%) and 56% (55%-57%) respectively, compared with Cape Town and eKurhuleni with 1-month persistence of 19% (18%-20%) and 8% (7%-9%), respectively (**Chapter 3, Appendix Table 1**).

Re-initiation

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

Group-based trajectory modeling

We identified three latent trajectory groups for FSW (BIC: -37,369, Entropy: 0.97, Shape parameter: cubic) and two groups for AGYW (BIC: -73,738, Entropy: 0.95, Shape parameter: quadratic). (**Chapter 3, Figure 4**)

For FSW, we identified “limited use,” “early cycling,” and “ongoing cycling” groups. 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 (**Chapter 3, Figure 4**).

For AGYW, we identified “limited use” and “ongoing cycling” groups. 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. **(Chapter 3, Figure 4)**

Correlates of discontinuation

Among FSW, there was no definitive relationship between 1-month persistence and the number of initiations. For Ngaka Modiri Molema, Nkangala, and OR Tambo, there appears to be a negative relationship between persistence and number initiated, but for Kenneth Kaunda and uMgungundlovu, there was an observed positive relationship. Among AGYW, 1-month persistence was negatively associated with an increase in initiation, and this pattern was seen across all sites **(Chapter 3, Figure 5)**. An increase of 100 initiations per month was associated with a 2% decrease in 1-month PrEP persistence (-0.02 (95% CI: -0.03, -0.01)).

For both FSW and AGYW, older age was associated with lower likelihood of discontinuation. Hazard of PrEP discontinuation was lower in more recent years for both populations. **(Chapter 3, Table 2).**

DISCUSSION

In this study, we described longitudinal patterns of PrEP use among over 40,000 FSW and AGYW in South Africa participating in a real-world PrEP service delivery program. The number of and proportion of eligible women who initiated PrEP increased each year for both FSW and AGYW. 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. By 7-months following initiation, less than 10% of both populations remained on PrEP. 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, whether that be “early cycling” or “ongoing cycling.” Persistence was negatively associated with the number of monthly initiations among AGYW, but there was no clear relationship among FSW, and those initiating in later years of the program did appear to have an improved likelihood of persisting on PrEP.

Across the study period, 19% of negative tests among FSW and 55% among AGYW resulted in initiation. The high proportion of AGYW who chose to initiate PrEP underlines the high HIV risk in this population in this setting. Although one might expect FSW to be more eager to initiate PrEP due to a perception that they have higher HIV risk than AGYW, possible explanations for the lower levels of initiation seen among FSW include 1) FSW have been using condoms as a trusted method of HIV prevention for years and may not see the need to change this or supplement it, 2) FSW experience

unstable housing and may be moving between places for work, which makes keeping track of a daily pill cumbersome, and 3) FSW face HIV-related stigma from other FSW and partners, and this stigma extends to a pill used for prevention.²³ Additionally, because women can test multiple times a year (FSW recommended to test quarterly), the denominator overestimates the number eligible and the proportion initiating in a given month is likely an underestimate of the proportion of FSW 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 the increases to the COVID-19 pandemic.²⁴ The proportion of eligible AGYW who initiated PrEP in our study was lower than in other studies. Data from HPTN 082 suggest that 95% of eligible AGYW in Cape Town, South Africa and Harare, Zimbabwe initiated PrEP.²⁵ This study, however, included only those AGYW who already reported interest in taking PrEP through a 36-item HIV prevention readiness measure.²⁵ Lower risk women were also screened out and were ineligible for participation, as compared to our study where all HIV-negative women accessing prevention services were eligible.²⁵ Another study of PrEP initiation and continuation among pregnant and postpartum women in antenatal care in Cape Town found that 84% of women initiated PrEP at their first antenatal visit.²⁶ While this study was integrated into a real-world clinical setting, a woman's motivation to begin PrEP during an antenatal visit is likely very high, given the high rate of HIV acquisition during pregnancy and the increased focus on health maintenance and preventative health during pregnancy.^{26,27}

Similar to what has been previously demonstrated in both clinical trials and clinic-based PrEP delivery settings in sub-Saharan Africa, persistence on PrEP among both FSW¹⁵ and AGYW^{16,28,29} in our study population was low, with over half discontinuing use 1-month after initiation. A recent study of similar programmatic data from the Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe (DREAMS) Initiative in Kenya found that about 37% of 1259 AGYW persisted on PrEP at 3 months.²⁸ Consistently, in our study, 33% of FSW and 24% of AGYW persisted on PrEP at 3 months. This study of DREAMS AGYW data also identified heterogeneity across program sites and found that older age was associated with improved persistence.²⁸ 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.¹⁹

In our study, only 9% of FSW and 3% of AGYW who discontinued PrEP re-initiated within one year. Capturing the occurrence of re-initiation, however, relies on the program linking records for the same woman correctly, and this number may be an underestimate of the true number of re-initiations. 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.^{30,31}

Many individuals in our study population experienced irregular engagement in PrEP services during the period, which based on our latent trajectory models we defined as “early cycling” and “ongoing cycling” among FSW and “ongoing cycling” among AGYW.

While the data on 1-month persistence are disheartening, it is clear that women are continuing to engage in PrEP use after this initial discontinuation. If we are able to 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 persistence 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, USA¹⁸ and gay men in New South Wales³², or have used PrEP adherence over time as the primary outcome rather than PrEP persistence. In the two studies conducted in high-resource settings^{18,32}, 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 of FSW and AGYW in South Africa, in which there were few consistent PrEP users. This suggests that PrEP use trajectories may also be influenced by sociostructural, economic, and political factors. In a study of trajectories of PrEP 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.²² In this study, individuals initiating PrEP received regular adherence counseling.²² 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 Guidelines³³, further resources may be needed to comprehensively and consistently evaluate PrEP readiness prior to initiation. Even with tailored adherence support, without a clear understanding and readiness on the part of the PrEP user not just to begin PrEP but to stay on it, PrEP pills will go unused at a non-trivial cost to the program, and there is a risk of the development of HIV drug resistance,³⁴ with women starting on PrEP, but not maintaining a therapeutic dose.

There are some important limitations of these analyses. First, individuals were characterized as part of the FSW or AGYW populations 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, approximately 5.7% of the 28,100 AGYW in the sample. 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 the two programs operate independently and that 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. While we believed these data to be missing completely at random, we did not have the ability to verify this assumption because of limited data availability. It is possible then that some bias may have been introduced due to missing data. Third, as noted above, the number of re-initiations captured may be an underestimate as it relied heavily on program staff

correctly linking records across time for the same woman. However, this is a process that is managed by case managers and nursing staff who know many of the women who come in to receive services by name. Finally, during the study period, the program shifted from monthly PrEP dispensation to multi-month dispensing. The details regarding this change in programming have been described previously.²⁰ For those months in which the woman had PrEP in her possession, but did not need to return for a visit, the routine PrEP register still documents that woman as being on PrEP. We therefore chose to keep our unit of analysis as monthly engagement with the program and/or 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 PrEP adherence, or 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).

CONCLUSION

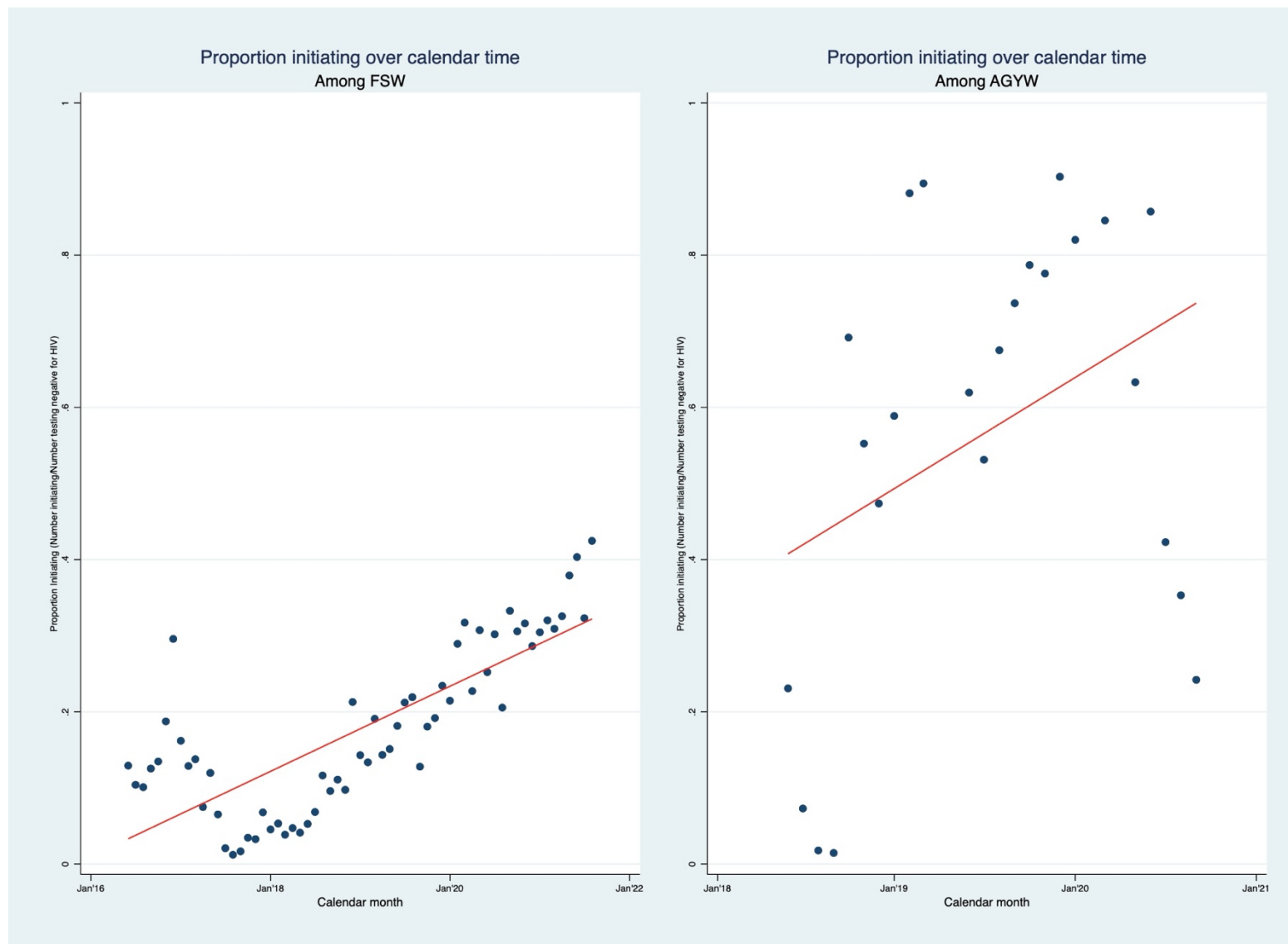
The results from these analyses reinforce that persistence on PrEP among young women at high-risk for HIV is low. We demonstrated here that cycling on and off PrEP is common, with early missed visits and inconsistent, but ongoing use. The traditional approach to capturing and documenting formal discontinuation and re-initiation events may be obfuscating these important patterns of PrEP use. While we are unable to unpack in this study individual-level characteristics of who specifically is represented in the different longitudinal trajectory groups, better understanding of these varying

patterns of PrEP use, including early and ongoing cycling, may help us tailor who is started on PrEP given limited resources and/or strategies to try to improve persistence for FSW and AGYW. A push to start as many people as possible on PrEP without consideration of 1) their readiness or their 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.

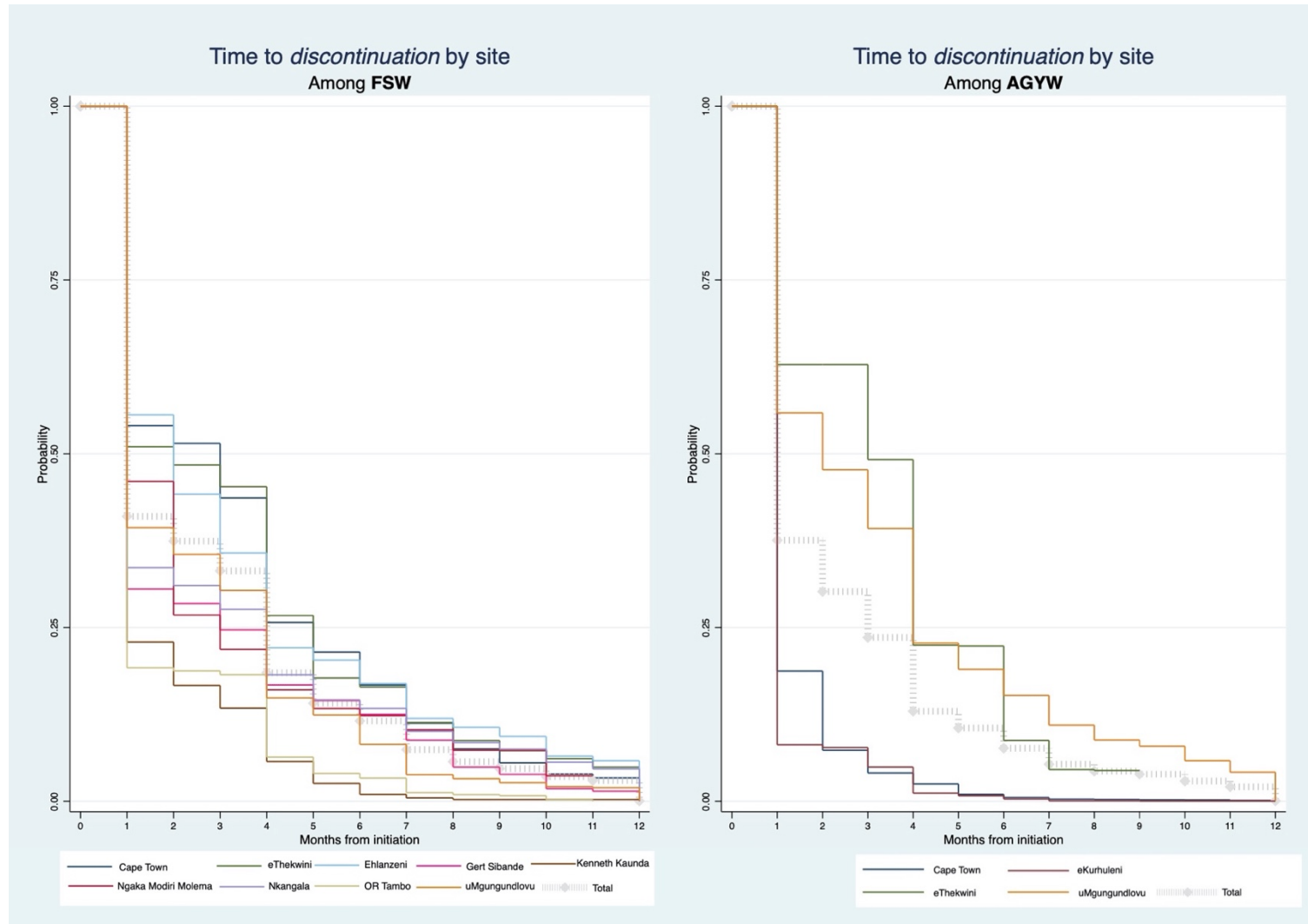
Chapter 3, Table 1. Characteristics of female sex workers (FSW) and adolescent girls and young women (AGYW) initiating PrEP through TB HIV Care between 2016 and 2021

	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)
eThekwini	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		
18 years old or younger	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)	

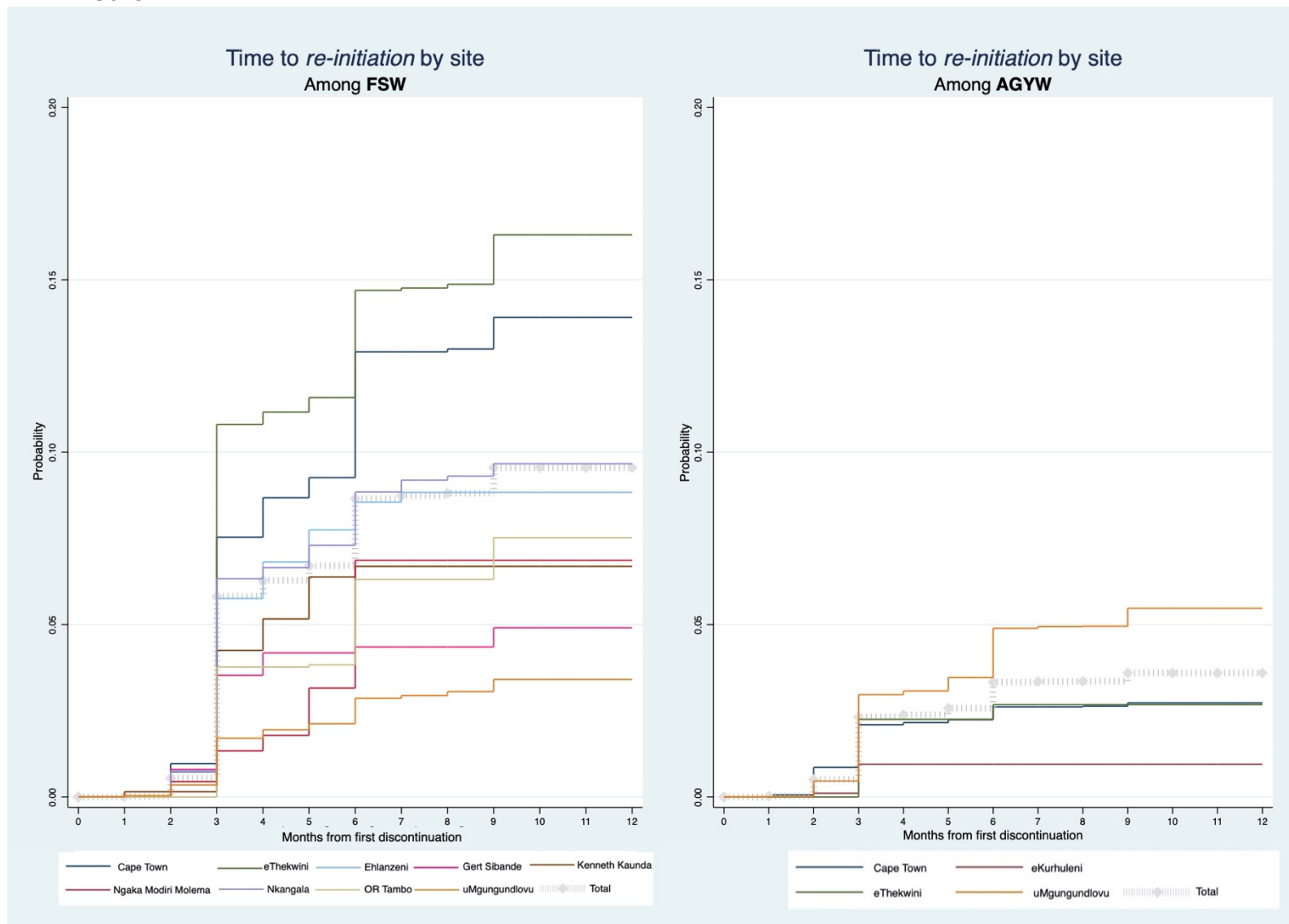
Chapter 3, Figure 1. Proportion of eligible HIV negative encounters initiating PrEP over time among female sex workers and adolescent girls and young women at TB HIV Care (2016-2021)



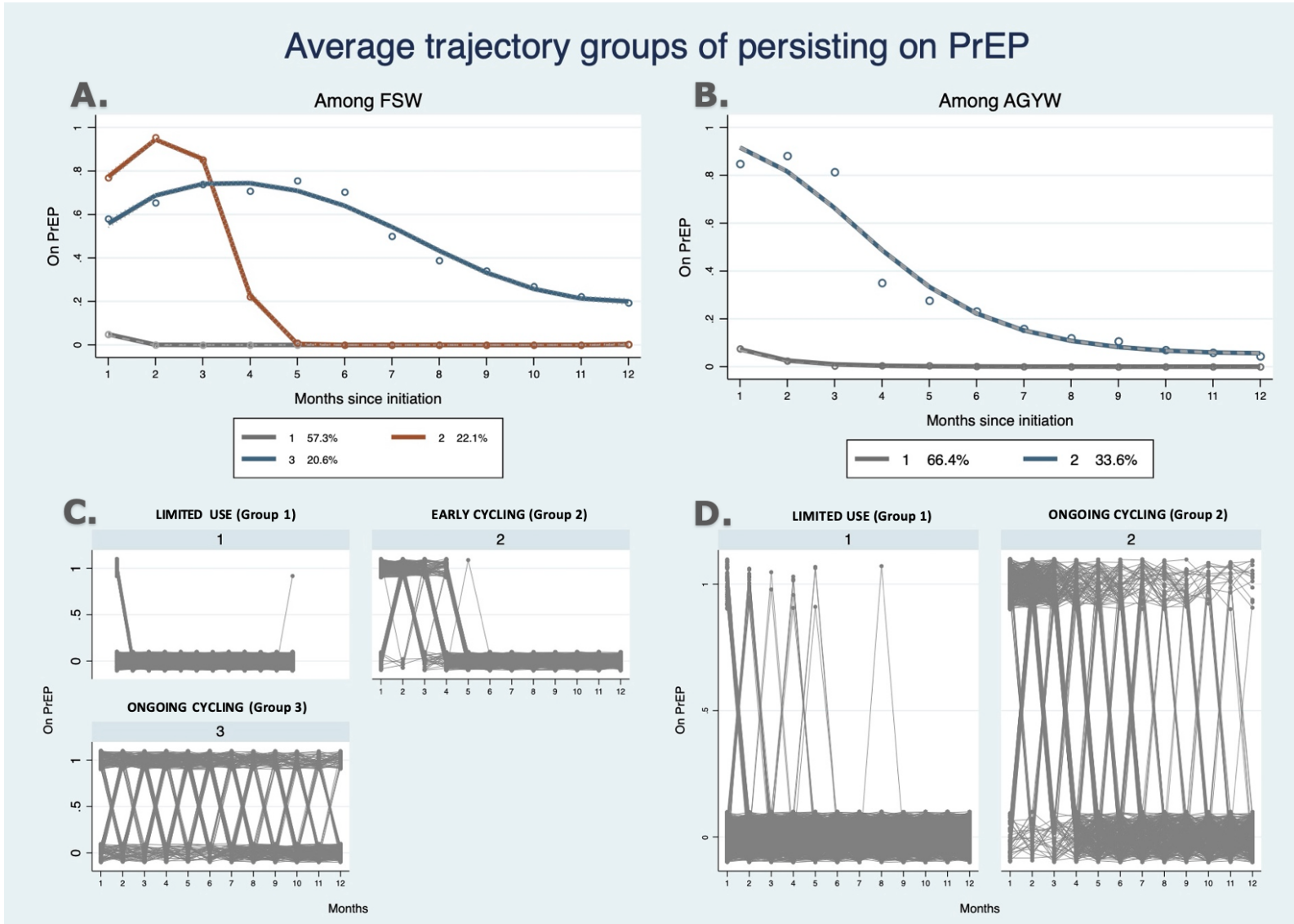
Chapter 3, Figure 2. Kaplan-Meier survival curves of the time from initiation to first discontinuation by site among female sex workers (n=12581) and adolescent girls and young women (n=28100) who initiated PrEP between 2016 and 2021 at TB HIV Care



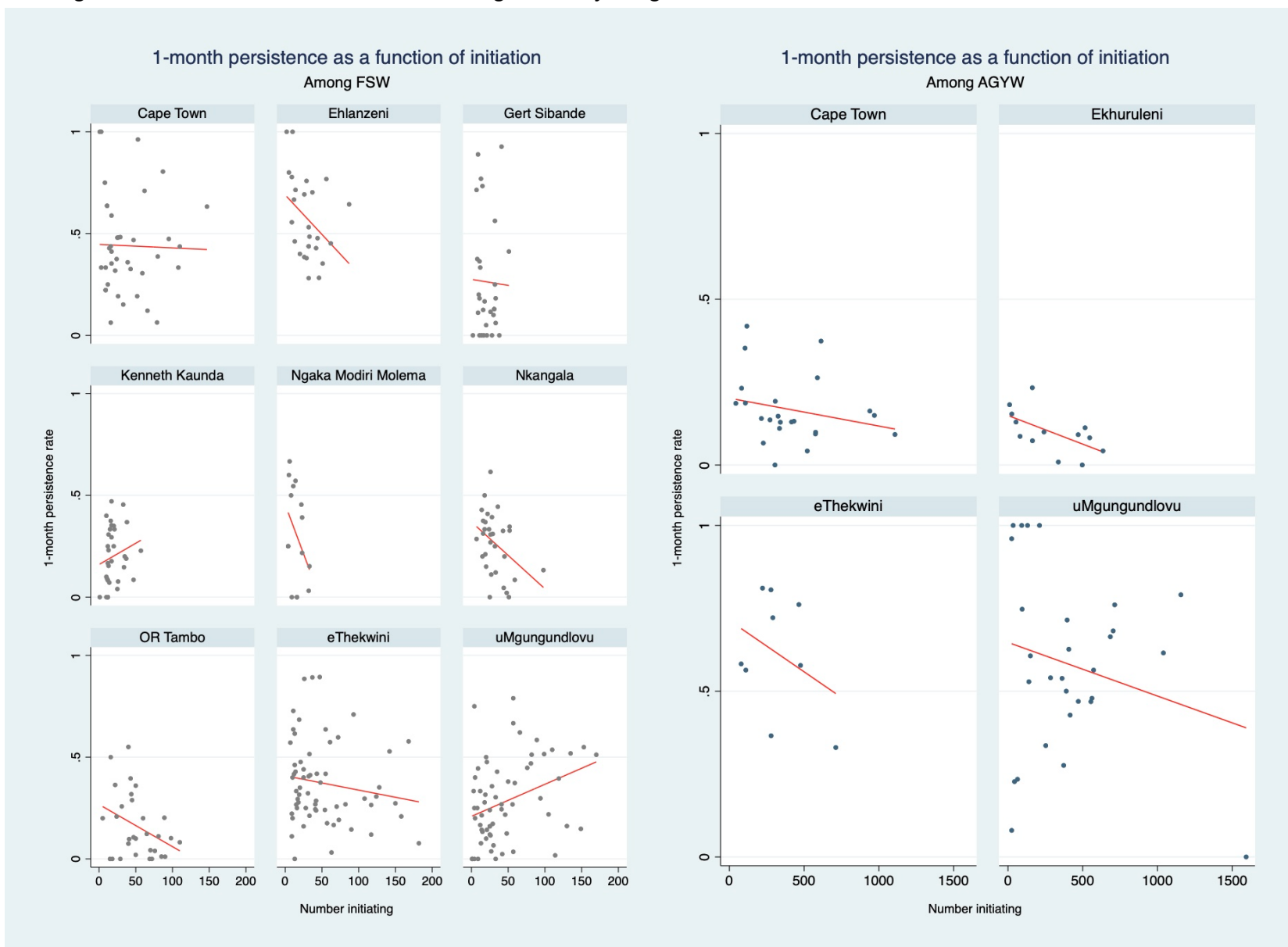
Chapter 3, Figure 3. Cumulative incidence curves of the time from discontinuation to re-initiation by site among female sex workers (n=12,581) and adolescent girls and young women (n=28,100) who initiated PrEP between 2016 and 2021 at TB HIV Care



Chapter 3, 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)



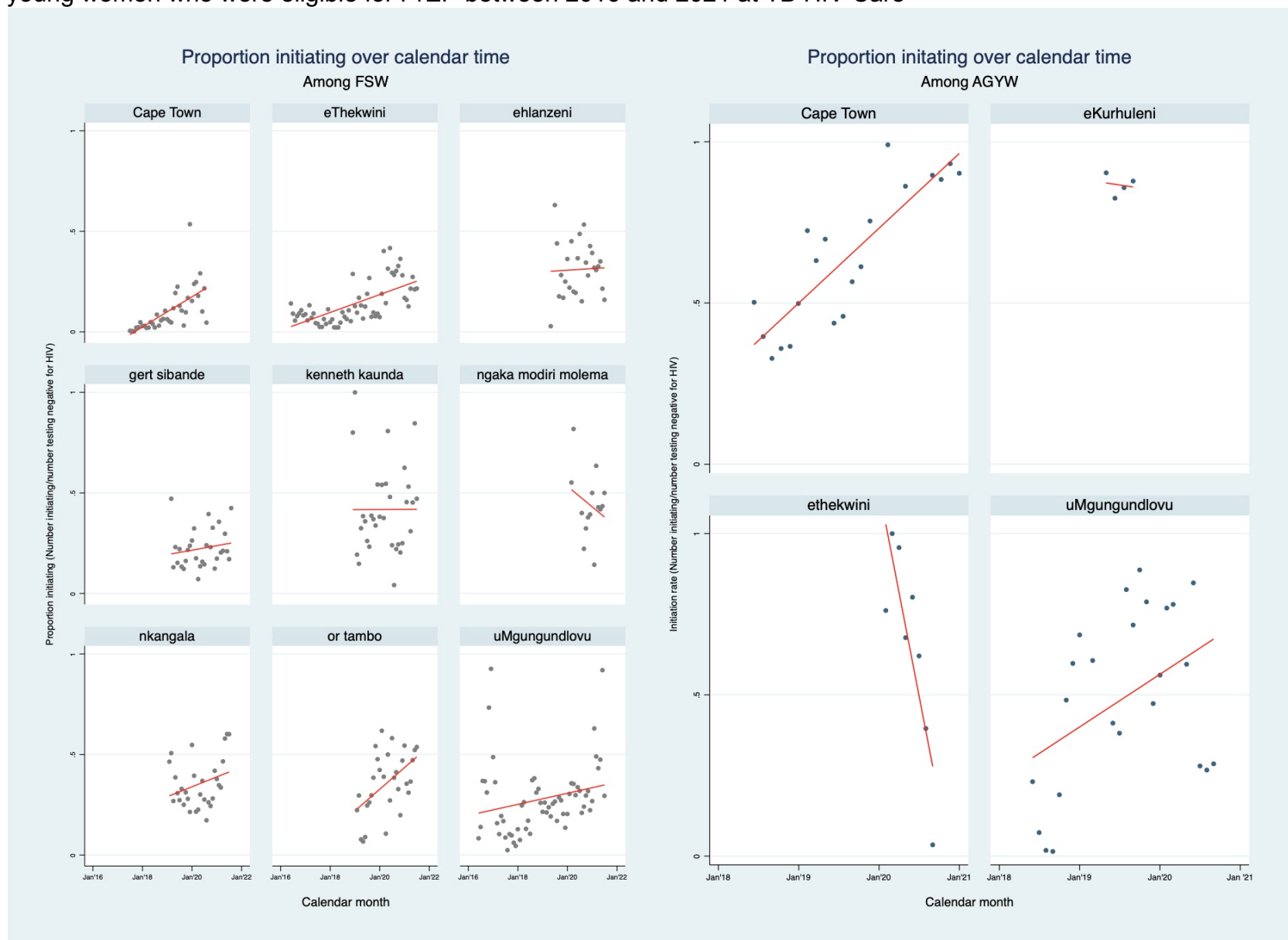
Chapter 3, Figure 5. Persistence on PrEP at 1-month plotted against the number of initiations seen in the program by site among female sex workers and adolescent girls and young women between 2016 and 2021 at TB HIV Care



Chapter 3, Table 2. Hazard of PrEP discontinuation among female sex workers and adolescent girls and young women initiating PrEP through TB HIV Care in South Africa 2016-2021

	FEMALE SEX WORKERS (n=12,581)	ADOLESCENT GIRLS AND YOUNG WOMEN (n=28,100)
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Age		
<25 years old	<i>ref</i>	<i>ref</i>
25+ years old	0.85 (0.83 - 0.87)	0.81 (0.77 - 0.84)
Year		
2016	<i>ref</i>	NA
2017	1.12 (1.01 - 1.24)	NA
2018	1.14 (1.04 - 1.24)	<i>ref</i>
2019	0.87 (0.80 - 0.94)	1.44 (1.38 - 1.50)
2020	0.90 (0.83 - 0.97)	0.88 (0.85 - 0.92)
2021	0.78 (0.72 - 0.85)	NA
Site		
Cape Town	<i>ref</i>	<i>ref</i>
eThekwini	1.13 (1.08 - 1.18)	0.23 (0.22 - 0.24)
Ehlanzeni	1.17 (1.11 - 1.26)	NA
Gert Sibande	1.63 (1.52 - 1.76)	NA
Kenneth Kaunda	2.30 (2.14 - 2.47)	NA
Ngaka Modiri Molema	1.45 (1.28 - 1.64)	NA
Nkangala	1.43 (1.35 - 1.52)	NA
OR Tambo	2.11 (2.00 - 2.23)	NA
uMgungundlovu	1.44 (1.37 - 1.51)	0.22 (0.22 - 0.23)
eKurhuleni	NA	0.71 (0.68 - 0.73)

Chapter 3, Appendix Figure 1. Proportion initiating over time by site among female sex workers and adolescent girls and young women who were eligible for PrEP between 2016 and 2021 at TB HIV Care



Chapter 3, Appendix Table 1. Kaplan-Meier estimates of discontinuation for 1-month, 4-month, and 7-month persistence on PrEP and cumulative incidence of re-initiation at 3-months, stratified by population (female sex workers and adolescent girls and young women) and site

DISCONTINUATION (SURVIVAL)					RE-INITIATION (CUMULATIVE INCIDENCE)	
		Time from <i>initiation</i> to discontinuation				Time from <i>discontinuation</i> to restart
	No. initiated	1-month	4-month	7-month	No. re-initiated	3-month
FSW	12581	0.41 (0.40 – 0.42)	0.18 (0.18 – 0.19)	0.07 (0.07 – 0.08)	1146	0.06 (0.05 – 0.06)
Cape Town	1486	0.54 (0.51 - 0.57)	0.26 (0.23 - 0.28)	0.11 (0.10 - 0.13)	191	0.08 (0.06 – 0.09)
eThekwini	3268	0.51 (0.49 - 0.53)	0.27 (0.25 - 0.28)	0.11 (0.10 - 0.13)	494	0.11 (0.10 – 0.12)
Ehlanzeni	813	0.56 (0.52 - 0.59)	0.22 (0.19 - 0.25)	0.12 (0.10 - 0.15)	68	0.06 (0.04 – 0.08)
Gert Sibande	629	0.31 (0.27 - 0.34)	0.17 (0.14 - 0.20)	0.09 (0.07 - 0.11)	30	0.04 (0.02 – 0.05)
Kenneth Kaunda	659	0.23 (0.20 - 0.26)	0.06 (0.04 - 0.08)	0.00 (0.00 - 0.02)	44	0.04 (0.03 – 0.06)
Ngaka Modiri Molema	226	0.46 (0.39 - 0.52)	0.16 (0.11 - 0.22)	0.10 (0.06 - 0.16)	15	0.01 (0.00 – 0.04)
Nkangala	988	0.34 (0.31 - 0.37)	0.18 (0.16 - 0.21)	0.10 (0.08 - 0.12)	90	0.06 (0.05 – 0.08)
OR Tambo	1593	0.19 (0.17 - 0.21)	0.06 (0.05 - 0.08)	0.01 (0.01 - 0.02)	118	0.04 (0.03 – 0.05)
uMgungundlovu	2919	0.40 (0.38 - 0.41)	0.15 (0.14 - 0.16)	0.04 (0.03 - 0.05)	96	0.02 (0.01 – 0.02)
AGYW	28100	0.38 (0.37 – 0.38)	0.13 (0.13 – 0.13)	0.05 (0.05 – 0.06)	985	0.02 (0.02 – 0.03)
Cape Town	9660	0.19 (0.18 - 0.20)	0.02 (0.02 - 0.02)	0.00 (0.00 - 0.00)	263	0.02 (0.02 – 0.02)
eThekwini	2890	0.63 (0.61 - 0.65)	0.22 (0.21 - 0.24)	0.05 (0.03 - 0.06)	77	0.02 (0.02 – 0.03)
uMgungundlovu	11866	0.56 (0.55 - 0.57)	0.23 (0.22 - 0.24)	0.11 (0.10 - 0.12)	610	0.03 (0.03 – 0.03)
eKurhuleni	3684	0.08 (0.07 - 0.09)	0.01 (0.01 - 0.02)	0.00 (0.00 - 0.00)	35	0.01 (0.00 – 0.01)

REFERENCES

1. UNAIDS. South Africa. 2022.
<https://www.unaids.org/en/regionscountries/countries/southafrica>.
2. Karim SSA, Baxter C. HIV incidence rates in adolescent girls and young women in sub-Saharan Africa. *Lancet Glob Health* 2019; **7**(11): e1470-e1.
3. UNAIDS. Ending AIDS: progress towards the 90–90–90 targets. UNAIDS Geneva, Switzerland; 2017.
4. UNAIDS. Empower young women and adolescent girls: fast-tracking the end of the AIDS epidemic in Africa. *Geneva: UNAIDS* 2015.
5. Dellar RC, Dlamini S, Karim QA. Adolescent girls and young women: key populations for HIV epidemic control. *J Int AIDS Soc* 2015; **18**(2 Suppl 1): 19408.
6. Birdthistle I, Tanton C, Tomita A, et al. Recent levels and trends in HIV incidence rates among adolescent girls and young women in ten high-prevalence African countries: a systematic review and meta-analysis. *Lancet Glob Health* 2019; **7**(11): e1521-e40.
7. UNAIDS. Global epidemic update: communities at the centre. 2019.
8. Kilburn K, Ranganathan M, Stoner MCD, et al. Transactional sex and incident HIV infection in a cohort of young women from rural South Africa. *AIDS* 2018; **32**(12): 1669-77.
9. Stoner MCD, Nguyen N, Kilburn K, et al. Age-disparate partnerships and incident HIV infection in adolescent girls and young women in rural South Africa. *AIDS* 2019; **33**(1): 83-91.
10. Ranganathan M, Heise L, Pettifor A, et al. Transactional sex among young women in rural South Africa: prevalence, mediators and association with HIV infection. *J Int AIDS Soc* 2016; **19**(1): 20749.
11. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363**(27): 2587-99.
12. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012; **367**(5): 411-22.
13. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367**(5): 399-410.
14. van der Straten A, Stadler J, Montgomery E, et al. Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. *PLoS One* 2014; **9**(2): e89118.
15. Eakle R, Gomez GB, Naicker N, et al. HIV pre-exposure prophylaxis and early antiretroviral treatment among female sex workers in South Africa: Results from a prospective observational demonstration project. *PLoS Med* 2017; **14**(11): e1002444.

16. Gill K, Pidwell T, Dietrich J, et al. A Demonstration Open Label Study to Assess the Acceptability, Safety and Use of Truvada Pre-exposure Prophylaxis in Healthy, HIV-Uninfected Adolescents, 15-19 Years of Age. Conference of the International AIDS Society. Paris, France; 2017.
17. Underhill K, Guthrie KM, Collieran C, Calabrese SK, Operario D, Mayer KH. Temporal Fluctuations in Behavior, Perceived HIV Risk, and Willingness to Use Pre-Exposure Prophylaxis (PrEP). *Arch Sex Behav* 2018; **47**(7): 2109-21.
18. Pyra M, Brewer R, Rusie L, Kline J, Willis I, Schneider J. Long-term HIV Pre-exposure Prophylaxis Trajectories Among Racial & Ethnic Minority Patients: Short, Declining, & Sustained Adherence. *J Acquir Immune Defic Syndr* 2022; **89**(2): 166-71.
19. Reed JB, Shrestha P, Were D, et al. HIV PrEP is more than ART-lite: Longitudinal study of real-world PrEP services data identifies missing measures meaningful to HIV prevention programming. *J Int AIDS Soc* 2021; **24**(10): e25827.
20. Rao A, Mhlophe H, Comins C, et al. Persistence on oral pre-exposure prophylaxis (PrEP) among female sex workers in eThekweni, South Africa, 2016–2020. *PLoS One* 2022.
21. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol* 2010; **6**: 109-38.
22. Stoner MCD, Rucinski KB, Giovenco D, et al. Trajectories of PrEP Adherence Among Young Women Aged 16 to 25 in Cape Town, South Africa. *AIDS Behav* 2021; **25**(7): 2046-53.
23. Kadiamada-Ibarra H, Hawley NL, Sosa-Rubi SG, Wilson-Barthes M, Franco RR, Galarraga O. Barriers and facilitators to pre-exposure prophylaxis uptake among male sex workers in Mexico: an application of the RE-AIM framework. *BMC Public Health* 2021; **21**(1): 2174.
24. Matambanadzo P, Busza J, Mafaune H, et al. "It went through the roof": an observation study exploring the rise in PrEP uptake among Zimbabwean female sex workers in response to adaptations during Covid-19. *J Int AIDS Soc* 2021; **24 Suppl 6**: e25813.
25. Celum C, Hosek S, Tsholwana M, et al. PrEP uptake, persistence, adherence, and effect of retrospective drug level feedback on PrEP adherence among young women in southern Africa: Results from HPTN 082, a randomized controlled trial. *PLoS Med* 2021; **18**(6): e1003670.
26. Joseph Davey DL, Mvududu R, Mashele N, et al. Early pre-exposure prophylaxis (PrEP) initiation and continuation among pregnant and postpartum women in antenatal care in Cape Town, South Africa. *J Int AIDS Soc* 2022; **25**(2): e25866.
27. Mellins CA, Chu C, Malee K, et al. Adherence to antiretroviral treatment among pregnant and postpartum HIV-infected women. *AIDS Care* 2008; **20**(8): 958-68.

28. de Dieu Tapsoba J, Zangeneh SZ, Appelmans E, et al. Persistence of oral pre-exposure prophylaxis (PrEP) among adolescent girls and young women initiating PrEP for HIV prevention in Kenya. *AIDS Care* 2021; **33**(6): 712-20.
29. Celum CL, Mgodini N., Bekker, L.-G., Hosek, S., Donnell, D., Anderson, P., Dye, B. J., Pathak, S., Agyei, Y., Fogel, J. M., Marzinke, M. A., & Delany-Moretlwe, S. PrEP adherence and effect of drug level feedback among young African women in HPTN 082. 10th IAS Conference on HIV Science. Mexico City, Mexico; 2019.
30. Hill LM, Maseko B, Chagomerana M, et al. HIV risk, risk perception, and PrEP interest among adolescent girls and young women in Lilongwe, Malawi: operationalizing the PrEP cascade. *J Int AIDS Soc* 2020; **23 Suppl 3**: e25502.
31. Shea J, Bula A, Dunda W, et al. "The Drug Will Help Protect My Tomorrow": Perceptions of Integrating PrEP into HIV Prevention Behaviors Among Female Sex Workers in Lilongwe, Malawi. *AIDS Educ Prev* 2019; **31**(5): 421-32.
32. Jin F, Amin J, Guy R, et al. Adherence to daily HIV pre-exposure prophylaxis in a large-scale implementation study in New South Wales, Australia. *AIDS* 2021; **35**(12): 1987-96.
33. Bekker LG, Brown B, Joseph-Davey D, et al. Southern African guidelines on the safe, easy and effective use of pre-exposure prophylaxis: 2020. *South Afr J HIV Med* 2020; **21**(1): 1152.
34. Dimitrov DT, Boily MC, Hallett TB, et al. How Much Do We Know about Drug Resistance Due to PrEP Use? Analysis of Experts' Opinion and Its Influence on the Projected Public Health Impact. *PLoS One* 2016; **11**(7): e0158620.

CHAPTER 4: The impact of implementation strategies on PrEP persistence among women at high-risk for HIV acquisition in South Africa: an interrupted time-series study

Amrita Rao¹, Hlengiwe Mhlophe², Anje Pretorius², Mfezi Mcingana², Jennifer Mcloughlin², Lily Shipp¹, Stefan Baral¹, Harry Hausler², Sheree Schwartz¹, Catherine Lesko¹

¹Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore USA

²TB HIV Care, Cape Town, South Africa

Corresponding Author: Amrita Rao, ScM

Email: arao24@jhu.edu

Tel. 617 780 8853

Address: 615 N. Wolfe St. E6534 Baltimore MD 21205

ABSTRACT

Background

Female sex workers (FSW) and adolescent girls and young women (AGYW) make up a disproportionate number of new HIV infections in South Africa. PrEP is freely available to FSW and AGYW in South Africa, but unique barriers challenge PrEP persistence and PrEP persistence remains low. TB HIV Care, a large South African non-profit providing PrEP to FSW and AGYW populations, has implemented multiple strategies to improve PrEP persistence, but their impact has not been evaluated.

Methods

We used an interrupted time series design to estimate a level change in the 1-month PrEP persistence associated with rollout of various PrEP implementation strategies (clinical mentoring for providers, mobile van PrEP provision, SMS PrEP refill reminders, SMS support texts, WhatsApp support groups, a case management approach, and a loyalty rewards program). We used routinely collected data from TB HIV Care program files between 2016-2021. Separate models using Poisson regression of the 1-month persistence were constructed for the FSW and AGYW programs. In secondary analyses, we tested the association between each of the strategies and 4-month persistence.

Results

The median 1-month persistence across the study period for FSW was 33% (IQR: 27%-40%). We found that SMS support texts and refill reminders were associated with a 33%

relative increase in 1-month persistence (95% CI: 1.18-1.50) and clinical mentoring for providers was associated with 12% relative increase (95% CI: 1.03-1.23) among FSW. The loyalty rewards program was negatively associated with 1-month persistence in the same population (95% CI: 0.67, 0.82). The strategies that were shown to be useful at promoting persistence at 1-month had no impact on persistence at 4-months. Among AGYW, the median 1-month persistence across the study period was 43% (IQR: 30%-54%). Due to concerns over threats to validity and simultaneous changes, it was not possible to assess the impact of the implementation strategies on persistence among AGYW.

Conclusions

SMS support, refill reminders and provider mentoring appeared to increase 1-month persistence. Identification and subsequent utilization of these beneficial strategies may improve the utility of PrEP overall to prevent new HIV infections among FSW.

Persistence remains a critical issue, however, and strategies to build on these gains longer term are needed.

Keywords: Pre-exposure prophylaxis for HIV prevention; Adolescent girls and young women; Female sex workers; Implementation strategies; Persistence

INTRODUCTION

Female sex workers (FSW) and adolescent girls and young women (AGYW) ages 15-24 years old in South Africa experience a disproportionately high incidence of HIV. Estimates suggest that there are as many as 13.2 new cases per 100 person-years among FSW^{1,2} and 2.5 per 100 person-years among AGYW.³ Young women in South Africa are between five and six times as likely as their male counterparts to be infected with HIV and make up close to one third of all new infections in the country.¹ Despite significant investment and progress made towards reducing the number of new infections globally, declines in new infections among young women have remained modest and unmet prevention needs have persisted, particularly across Southern Africa.⁴

Pre-Exposure Prophylaxis for HIV Prevention (PrEP) has emerged as a key biomedical intervention that can be used discreetly and autonomously to prevent new HIV infections, in tandem with other HIV prevention strategies.^{5,6} PrEP has been shown to be efficacious, reducing HIV acquisition by approximately 90% among women in trial settings.^{7,8} Among cisgender women particularly, success of this prevention tool is contingent on consistent medication adherence, with increased protection conferred by higher levels of adherence. PrEP adherence is closely linked with and made possible by PrEP persistence, or returning to pick up regular PrEP refills. Despite the free availability of PrEP to FSW and AGYW through the South African national HIV program⁹, unique barriers exist that challenge PrEP persistence. Barriers to consistent use of PrEP include limited understanding of HIV risk^{10,11}, concerns over side effects¹²,

imperfect provider knowledge and inadequate communication with patients^{13,14}, and stigma from the community^{13,14}. Strategies to alleviate some of these barriers among young women have been implemented by programs, but have largely not been evaluated for relative effectiveness.

TB HIV Care is a South African non-profit organization that provides a range of sexual and reproductive health services to FSW, AGYW, and other key populations, including people who use drugs and transgender women.¹⁵ TB HIV Care began providing PrEP to FSW in 2016 and AGYW in 2018. As of 2022, the program has initiated more than 40,000 women at high-risk for HIV on PrEP and serves as the largest PrEP provider to young women in the country.

As part of PrEP roll-out, TB HIV Care has been utilizing several different strategies designed to promote PrEP persistence and to alleviate barriers to ongoing PrEP use. These implementation strategies have been chiefly adapted from existing strategies that have been shown to be effective in improving HIV treatment retention¹⁶⁻¹⁸ but have not yet been evaluated in the prevention space. Using routinely collected program records from TB HIV Care, there is a unique opportunity to evaluate the impact of different implementation strategies on PrEP persistence in a large scale real-world setting.

METHODS

Study Design and Setting

We evaluated PrEP service outcomes (PrEP initiation and persistence) conducted by TB HIV Care between June 2016 and April 2021 and May 2018 and September 2020 for the FSW and AGYW programs, respectively, corresponding to the start of PrEP delivery for each population and availability of complete data. During the study period, the FSW program operated out of nine sites in five provinces: 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), and the AGYW program operated out of seven sites in four provinces: KwaZulu Natal (eThekweni, uMgungundlovu, Zululand, uThukela), Gauteng (Ekurhuleni), Eastern Cape (OR Tambo), and Western Cape (Cape Town) **(Chapter 4, Figure 1)**. We analyzed data separately for FSW and AGYW. While there is overlap in implementation strategies used between the two, the programs work independently with different standard operating procedures for PrEP service delivery and different management structures. The target populations served by the two programs have many of the same risks for HIV but are often recruited from different settings and may have different perceptions and knowledge of HIV risk.

Participants

The study population includes FSW and AGYW who initiated PrEP through TB HIV Care during the study period. FSW are women who make the majority of their income exchanging sex for money. AGYW are girls and young women 15-24 years old who are at high-risk for HIV and are recruited to initiate PrEP from schools, higher education institutions, and community organizations where young women are known to congregate.

Individuals were eligible to begin PrEP during this period if they were receiving other services from TB HIV Care, including sexually transmitted infection testing, pregnancy testing, HIV testing, and/or family planning, and tested negative for HIV.

Implementation strategies

The implementation strategies and clinical support interventions utilized by TB HIV Care to promote PrEP persistence are described in greater detail in the Appendix. (**Chapter 4, Appendix Table 1**) Briefly, they include the following: 1) clinical mentoring for providers (weekly meetings conducted with PrEP providers, led by a nurse clinician or clinical trainer to review best practices for PrEP provision), 2) mobile van PrEP provision (decentralized delivery of PrEP in the community using a TB HIV Care mobile van), 3) SMS PrEP refill reminders (text messages sent one week before and one day before scheduled refill), 4) SMS support texts (generic support messages designed to empower and promote self-efficacy), 5) WhatsApp support groups (groups of PrEP users where members can discuss successes and challenges in using PrEP), 6) a case management approach (dedicated TB HIV Care staff assigned to individuals to provide support and guidance with regard to HIV prevention care), and 7) a loyalty rewards program (incentives in the form of airtime, or credit that is used to make calls, send texts, and access online services, provided to individuals at initiation and upon returning for subsequent PrEP visits). Details around which sites implemented each of the strategies can be found in **Chapter 4, Table 1**. The strategies included here target **1)** the individual PrEP user (SMS refill reminders, SMS support texts, WhatsApp support groups, case management approach, loyalty rewards program), **2)** providers (clinical

mentoring for providers, and **3)** the health system architecture (mobile van PrEP provision).

Outcome

The primary outcome of PrEP persistence at one-month was defined as whether or not a client returned to pick up her PrEP refill one-month following initiation. This information was obtained from an electronic program register that is kept up-to-date with each PrEP-related clinical encounter a client has with the program. ITS studies tend to be best at detecting effects of interventions on short-term outcomes that are expected to change relatively quickly.¹⁹ Given early evidence that about half of women are dropping out after 1-month²⁰, we felt this endpoint would be the most relevant outcome.

For the analysis, data at the individual-level were aggregated to produce monthly, site-specific counts of the number of women who picked up their 1-month PrEP refills and counts of the number of women who initiated PrEP in the prior month (who would be expected to pick up a PrEP refill).

Statistical Analysis

We plotted 1-month persistence by calendar month using linear splines to describe trends in persistence over time. The final linear spline models and placement of the knots were selected based on visual inspection of the data and a comparison of different model Akaike information criteria (AICs). The slopes from these linear models represent the change in 1-month persistence per 1-month change in calendar time

during the specified period. We utilized an interrupted time series design to assess the impact of implementation strategies on PrEP persistence, fitting a Poisson regression model for number of completed 1-month PrEP visits that included a term for calendar months since the start of the study period, indicators representing whether each of the implementation strategies was in place for that month, and number of COVID cases in South Africa in each calendar month. We also included an offset for the number of individuals who initiated PrEP in the prior month to account for any changes in the number initiating over time.

The study period overlaps with the COVID-19 pandemic, which has been shown in some instances to have caused disruption to HIV service delivery.^{21,22} In South Africa, HIV prevention and treatment services were deemed essential and continued to operate during the pandemic. To account for changes that may have occurred in service delivery or engagement in services due to COVID-19, we included monthly case counts of COVID-19 obtained from the National Institute of Communicable Diseases (NICD) in the final models.²³ The assumption of this approach is that both formal (e.g., restrictions to public transportation schedules) and informal (e.g., individuals' risk perception and self-imposed social distancing) restrictions on PrEP pick-ups would be a function of local COVID-19 transmission levels.

Individuals who initiated PrEP prior to implementation of a given strategy contributed to the estimate of persistence in the absence of that strategy. Individuals who initiated at a site after a strategy or strategies had been implemented contributed to the estimate of

PrEP persistence in the presence of the strategy. We modeled the impact of each strategy on the 1-month persistence.

The statistical model used to assess the impact of the different implementation strategies took the following form:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_1 + \beta_3 X_2 + \beta_4 X_3 + \beta_5 X_4 + \beta_6 (COVID) + offset(person\ time)$$

where Y represents the number of individuals persistent on PrEP at one-month at each site, β_0 represents the persistence at T=0 (prior to the implementation of any of the strategies), β_1 represents the change in the persistence associated with time, β_2 to β_5 represent the independent level changes following implementation of each of the different strategies, and β_6 represents the level change associated with monthly COVID cases reported in South Africa.

We did not anticipate estimates of 1-month PrEP persistence to be autocorrelated, since they were dependent on independent observations – individuals initiating PrEP. To check this assumption, we examined the plot of the residuals.

Secondary Analyses

We conducted three secondary analyses. First, we ran the same original model using persistence on PrEP at four months as the outcome. Second, we adjusted for the total number of women testing negative (eligible for PrEP) each month to account for changing burden on the program. Third, we removed the first introduction for any

strategy that had two different introductions, that is any strategy that initially started and then re-started in order to evaluate the strategy once it was in full effect.

Timing of PrEP delivery and implementation of each of the strategies

Part of answering this research question was ascertaining the timing of implementation of different strategies and determining which strategies we could evaluate. We could not evaluate the impact of strategies for which there were 0 months of pre-strategy data (i.e. the strategy was implemented at the start of PrEP implementation), and therefore we excluded these strategies from our analysis. Additionally, when strategies were implemented as a group, we had to consider the joint effects of these strategies, as it was not possible to disentangle their independent effects. **(Chapter 4, Appendix Table 2)**

RESULTS

Female Sex Worker (FSW) program

The median 1-month persistence across the study period for FSW was 33% (IQR: 27%-40%). At the start of PrEP provision (June 2016-February 2017), there was a 6% decrease in persistence per month (slope: -0.06, 95% CI: -0.09, -0.04). Following this, between February 2017 and January 2018 there was a 1.5% increase in persistence per month (slope: 0.015, 95% CI: -0.005, 0.03). From February 2018 to September 2020, PrEP persistence was fairly stable (slope: 0.002, 95% CI: -0.001, 0.01). **(Chapter 4, Figure 2)**

Given insufficient pre- and post- strategy data, we could not evaluate the impact of mobile van PrEP provision (0 months of pre-strategy data) and WhatsApp support groups (not implemented in the FSW program) on PrEP persistence for FSW. SMS PrEP refill reminders and SMS support texts were implemented together and therefore evaluated as a package. We evaluated the independent impact of clinical mentoring for providers, SMS refill reminders and support texts, the case management approach, and the loyalty rewards program among FSW. **(Chapter 4, Appendix Table 2)**. The FSW-specific statistical model we used is represented by the following equation:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_1 + \beta_3 X_2 + \beta_4 X_3 + \beta_5 X_4 + \beta_6 (COVID) + offset(person\ time)$$

where X_1 represents clinical mentoring for providers, X_2 represents SMS PrEP refill reminders and support texts, X_3 represents the case management approach, and X_4 represents the loyalty rewards program.

Data from the nine different FSW sites were included for a total of 299 site-months and 11,020 total initiations. SMS support texts and refill reminders was associated with a 33% relative increase in 1-month persistence (95% CI: 1.18-1.50) and clinical mentoring for providers was associated with a 12% relative increase (95% CI: 1.03-1.23), after adjusting for the impact of the other strategies and monthly COVID-19 cases. The analysis suggested no effect of the case management approach (95% CI (0.92, 1.13)). The loyalty rewards program was negatively associated with persistence (95% CI (0.67, 0.82)). **(Chapter 4, Figure 3; Chapter 4, Table 2)**

Secondary Analyses

At the start of the study period, the model-estimated 4-month PrEP persistence was only 16%. The strategies that were shown to be useful at promoting persistence at 1-month had no impact on persistence at 4-months. We found no appreciable differences after 1) adjusting for the number of women testing negative for HIV or 2) removing the first introduction of the loyalty rewards program. **(Chapter 4, Table 2)**

Adolescent Girls and Young Women (AGYW) program

The median 1-month persistence across the study period for AGYW was 43% (IQR: 30%-54%). Unlike what was observed in the FSW program, persistence increased by 5% per month at the start of PrEP implementation, May 2018-Dec 2018 (slope: 0.05, 0.00-0.09). There was then an observed decrease of 11% per month for a 6-month period between December 2018 and May 2019 (slope: -0.11, -0.21, -0.02), before the trend in persistence appeared to eventually rebound and increase by 2% per month (slope: 0.02, 0.01, 0.04) **(Chapter 4, Figure 2)**.

For the AGYW program, there was insufficient pre- and post- strategy data to evaluate any of the strategies, and it was therefore not possible to develop an interrupted time-series model for the AGYW program. The reasons for insufficient data include 1) limited pre-strategy data (clinical mentoring for providers, mobile van PrEP provision, SMS support texts were implemented upon program start), 2) the strategy was never implemented among AGYW or implemented after the study period (loyalty rewards program), or 3) the threats to validity, including simultaneous increases in the number

initiating PrEP and changes to how data were collected, posed were too strong and any inference drawn from the analysis would be questionable (SMS refill reminders, WhatsApp support groups, and the case management approach).

DISCUSSION

In this study, we evaluated the impact of several implementation strategies on PrEP persistence in a large-scale PrEP delivery program in South Africa. During the study period, persistence appears to improve over time for the AGYW program and, to a more minor extent, the FSW program. The FSW program experienced some increases, but also quite a bit of fluctuation in persistence after January 2018. Despite these improvements, persistence at 1-month was low, with less than half of those who initiated remaining on PrEP for both populations over the course of the study period. In this study, among FSW, implementation of clinical mentoring for providers and SMS support texts and refill reminders were positively associated with PrEP persistence, while the loyalty rewards program was negatively associated with PrEP persistence. Because of insufficient pre- and post- strategy data and other threats to validity, we were unable to evaluate PrEP persistence support strategies for the AGYW program. The results presented here begin to elucidate which specific strategies may have an impact on PrEP persistence among FSW in a real-world setting and can immediately inform more effective service delivery. There remains a need to evaluate similar strategies to improve PrEP persistence among AGYW.

While the implementation strategies utilized by TB HIV Care have been adapted from existing strategies that have been effective in improving HIV treatment retention, persistence in HIV prevention programs and adherence to PrEP pose unique and multifactorial challenges that need to be independently explored, especially for this population at high-risk for HIV acquisition.^{10,13,14,24-29} The feasibility and acceptability of a few, limited strategies to promote PrEP persistence have been evaluated^{30,31}, including one study among sexual and minority youth in the United States that found high acceptability of a broad range of mHealth interventions to promote HIV testing and PrEP use, including SMS messages.²⁶ Implementation strategies have been largely untested in terms of relative effectiveness.³²⁻³⁵

SMS support texts and refill reminders were shown in the present study to be effective at improving PrEP persistence among FSW. SMS messages may address the proximal, patient-level barriers of self-efficacy and remembering to return for PrEP refills.

Examples of some of the messages TB HIV Care uses include: “Congratulations on making the decision to take control of your health! Have you taken your pill?” or “If you have been taking your pill every day, you are now protected! Well done! Keep going to stay healthy.” Previous study results are mixed in terms of the effectiveness of SMS messages on persistence or adherence to medication, both among people living with HIV and for HIV prevention. A systematic review of the effectiveness of mobile text reminders among people living with HIV¹⁶ indicated a similar positive association between text messaging and adherence to medication.¹⁷ On the other hand, a recent randomized controlled trial of 348 young adult women in Kenya found no difference in

PrEP adherence between those assigned to receive SMS reminders and those who did not.³⁶ This observed difference in results between the RCT and our study could be in part explained by differences in study populations (young adult women in Kenya vs. FSW in South Africa), the study design (RCT vs. ITS), the content or dose of the strategy (e.g. the messages themselves or the frequency), or the operational definition of the outcome.³⁶ The study in Kenya looked at electronically monitored adherence over 24 months, while our study looked at 1-month persistence.³⁶

Clinical mentoring for providers was also shown to improve early PrEP persistence. Mentoring for providers may increase provider knowledge of PrEP, reduce potential stigma, and improve patient-provider communication.^{10,13,14,27} Providers serving the FSW program include HAST (HIV/AIDS, TB, and STI) counsellors (n~1-4 per site), who have the most interaction with the women and provide most prevention services, and professional nurses and nurse counselors (n~2-5 per site), who confirm PrEP eligibility and support the initiation and persistence process. Other staff involved in providing and supporting PrEP use include social workers, social auxiliaries (personnel that support social workers), case managers, drivers of the mobile vans, peer coordinators, and peer educators. Providers serving the AGYW program similarly include HAST counselors (n~10-40 per site) and clinical nurses and nurse coordinators (n~4-15 per site). A mixed methods study of clinical mentoring for nurse-initiated management of antiretroviral therapy in South Africa found that clinical mentors strengthened healthcare delivery and improved patient satisfaction.¹⁸

Surprisingly, we found that the loyalty rewards program was negatively associated with 1-month persistence. There were two introductions of the rewards program during the study period. It was initially started in early 2020, but then de-implemented in order for the program team to refine strategy implementation. We removed the first introduction in a secondary analysis to look exclusively at the impact of the final version of the rewards program and observed no difference. As with all of the strategies assessed in these analyses, there was no way to measure who was exposed or received the different strategies, or the fidelity of implementation. Based on program feedback, we have learned that this strategy was among one of the hardest to implement and it is possible that those who were eligible to participate in this strategy were not exposed to it. Further research, including that which studies implementation fidelity, is needed to understand the impact of this strategy and the others on PrEP persistence.

We found no effect of these strategies on 4-month persistence, suggesting a lack of durability of these strategies on longer term persistence. SMS refill reminders are sent one week before and one day before a scheduled refill and generic SMS support messages are sent weekly. The dose/frequency of contact remains consistent even after the first month. It is possible that the messaging helps motivate the individual to come back at one month, but is insufficient at overcoming other barriers and obstacles at four months (e.g. distance to get to clinic or mobile van, time to pick up refill, risk perception, etc.). For clinical mentoring for providers, the dose/frequency also remained constant, but further research is needed to understand if providers were focusing more

on the immediate, stark problem of follow-up at 1-month rather than longer term persistence.

There were some key challenges that threatened the validity of an interrupted time series model for AGYW, making development of a credible model infeasible.

Specifically, there were challenges posed by history (timing of strategy introduction), instrumentation and testing, and selection.³⁷ **History:** In October 2020, the AGYW program underwent several changes. Three new sites were introduced: Zululand, Utukhela, and OR Tambo. The program dramatically expanded to hit much higher initiation targets across all sites, and in some places tripled the number of women initiating. This change occurred at the same time as a large recruitment drive to increase the number of staff across the program to meet the increasing demand.

Instrumentation and testing: Additionally, a new data system was put into place to track clinical visits over time among women initiating PrEP with the program, replacing the existing PrEP register. The program switched over to the new system immediately to avoid dual reporting systems. According to program administrators, it took data entrants and managers about three months (October-December 2020) to learn and grow accustomed to the new data management system. Therefore, at the same time that there was a rapid increase in the number of initiations, there were documented errors during this period in the number attending their one-month visit. By January 2021, the program had put into place automated checks to flag discrepancies and confidence in the system improved. **Selection:** While we do not have the data to assess whether there were changes in the characteristics of those initiating before and after the change

in program targets, it is possible that those who were early adopters of PrEP were different in how likely they were to be persistent on PrEP compared with those who were reached in the much broader campaigns. The AGYW sites that implemented SMS refill reminders, WhatsApp support groups, and the case management approach either started each strategy at approximately the same time as these other program changes or had limited or no post-strategy data. Because of these threats to validity, we were unable to develop an interrupted time series model for the AGYW program, but we reported these results in the spirit of full transparency.

Despite these challenges, this study represents a unique opportunity to harness routinely collected data and real-world changes to implementation to better understand and improve PrEP delivery. Traditional data collection strategies such as community-based trials and cohorts can provide insights into efficacy but are limited by their highly controlled settings and can be costly. Even with the resources to support a trial, the controlled setting cannot replicate the real-world conditions faced by programs delivering PrEP (e.g. competing priorities and limited resources, changing targets, etc.), limiting the utility and the external validity of trial results. The use of an interrupted time-series, quasi-experimental design compared to a controlled trial means that we were able to assess more accurately the program-relevant implications of the strategies being evaluated. Routinely collected data can provide timely insights about different service delivery models and strategies to support provider implementation or client use, including key opportunities and limitations. The use of real-world routinely collected data also poses major challenges. We were limited by the timing of strategy introduction and

therefore could not evaluate strategy impact among AGYW. In a donor-funded program, decisions are often driven by external program targets and changes, both increases and decreases, in funding. From the program-perspective, simultaneous changes are common and make sense: an increase in program targets triggers an increase in the number of program sites and recruitment of new staff to meet the increased patient load, which in turn also triggers brainstorming of new ways to improve tracking of data and client management. Researchers aiming to use routinely collected data and take advantage of quasi-experimental approaches should anticipate and be able to account for these types of changes.

There are some important strengths of this analysis. In an ITS, we take advantage of time-series data, or a continuous sequence of observations on a population taken over time. This time-series is used to establish an underlying trend, which is then “interrupted” by a strategy or intervention at a known time. The hypothetical scenario in which the strategy had not occurred and the trend continues unchanged serves as the counterfactual.^{19,37} Where possible, we took advantage of both multiple baselines and sites that did not implement certain strategies. Using multiple baselines allowed us to make use of different units, or in our case different program sites, receiving the strategies at different time points. Because these units implemented the strategies at different points in calendar time, multiple baselines increased our confidence that any post-strategy changes are in fact due to the strategy under study and not due to co-occurring changes. Use of sites that never implemented a strategy increased our understanding of what would have happened in the absence of the strategy, without

solely relying on the assumption that the pre-strategy trend would have continued unchanged.

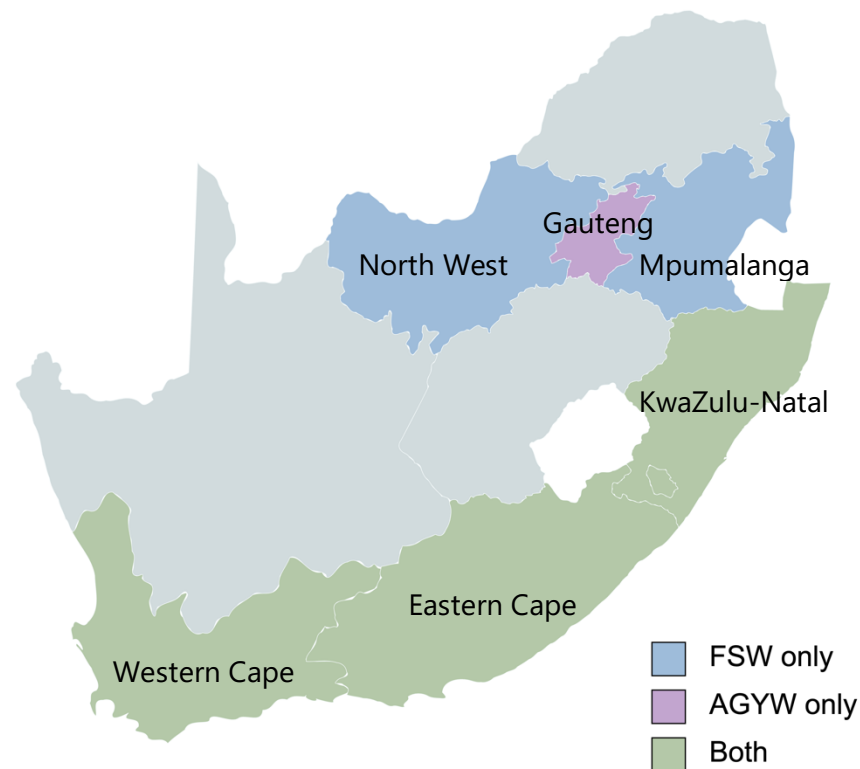
There are a few key limitations of this study. As noted, we were unable to evaluate the impact of strategies within the AGYW program, as well as mobile van PrEP provision among FSW due to the timing of introduction and timeframe studied. We were also unable to tease apart the impact of SMS support texts from SMS refill reminders, as these were implemented at the same time across the sites. While these are limitations of the analysis, threats to validity would have been too strong otherwise, potentially invalidating model results. The use of quasi-experimental approaches necessitates a reliance on real-world data, and though imperfect, means that the inferences that we were able to make have greater external validity.³⁸ It is possible that there were other changes that coincided with implementation of the strategies, though we carefully reviewed any other simultaneous changes that were occurring in the program. We anticipated the COVID-19 pandemic might alter PrEP use, and we attempted to adjust for possible service disruptions by adjusting for local COVID-19 case rates. However, we did not observe any substantial changes in PrEP persistence associated with the introduction or trajectory of COVID-19 in South Africa, possibly because HIV prevention services were deemed essential and not subject to any “lockdown” restrictions. Because of limited availability of pre and post strategy data, a simplifying assumption of the ITS model was that the underlying trend was linear. On inspection of the data, there was some non-linearity in the underlying trend, and this may have impaired our ability to detect level-changes. We evaluated several strategies, and it is possible that we

detected a significant positive or negative effect by chance. As a final limitation, the underlying population under study could have been changing over time. We were unable to assess this, as we did not have access to data on individual characteristics, e.g. demographics and behavioral characteristics. It is our belief that if the population was changing over time that it would have included a greater proportion of those who were less engaged in the program and more likely to drop-off at one month. While the interrupted time series design is primarily threatened by changes to population characteristics that coincided with the implementation of these strategies, we believe that this threat is less likely due to the varying implementation start dates of these strategies, both across strategies and across sites.

CONCLUSION

HIV incidence is disproportionately high among FSW and AGYW in South Africa. PrEP exists as a key opportunity to provide women with an additional HIV prevention tool, but the little data that do exist suggest real implementation challenges: initiation remains low, and many women discontinue use shortly after starting. In this study, we harnessed real-world routinely collected data from the largest PrEP provider in South Africa to identify that SMS refill reminders and support texts and clinical mentoring for providers may improve PrEP persistence at one month. While this is encouraging, the identified strategies had no impact on persistence at four months, suggesting that further research is needed to understand why women are stopping PrEP and what can be done to support them if they want to stay on PrEP for longer periods of time.

Chapter 4, Figure 1. Map of South African provinces where TB HIV Care operates PrEP delivery programs for female sex workers (FSW) and adolescent girls and young women (AGYW), 2016-2021



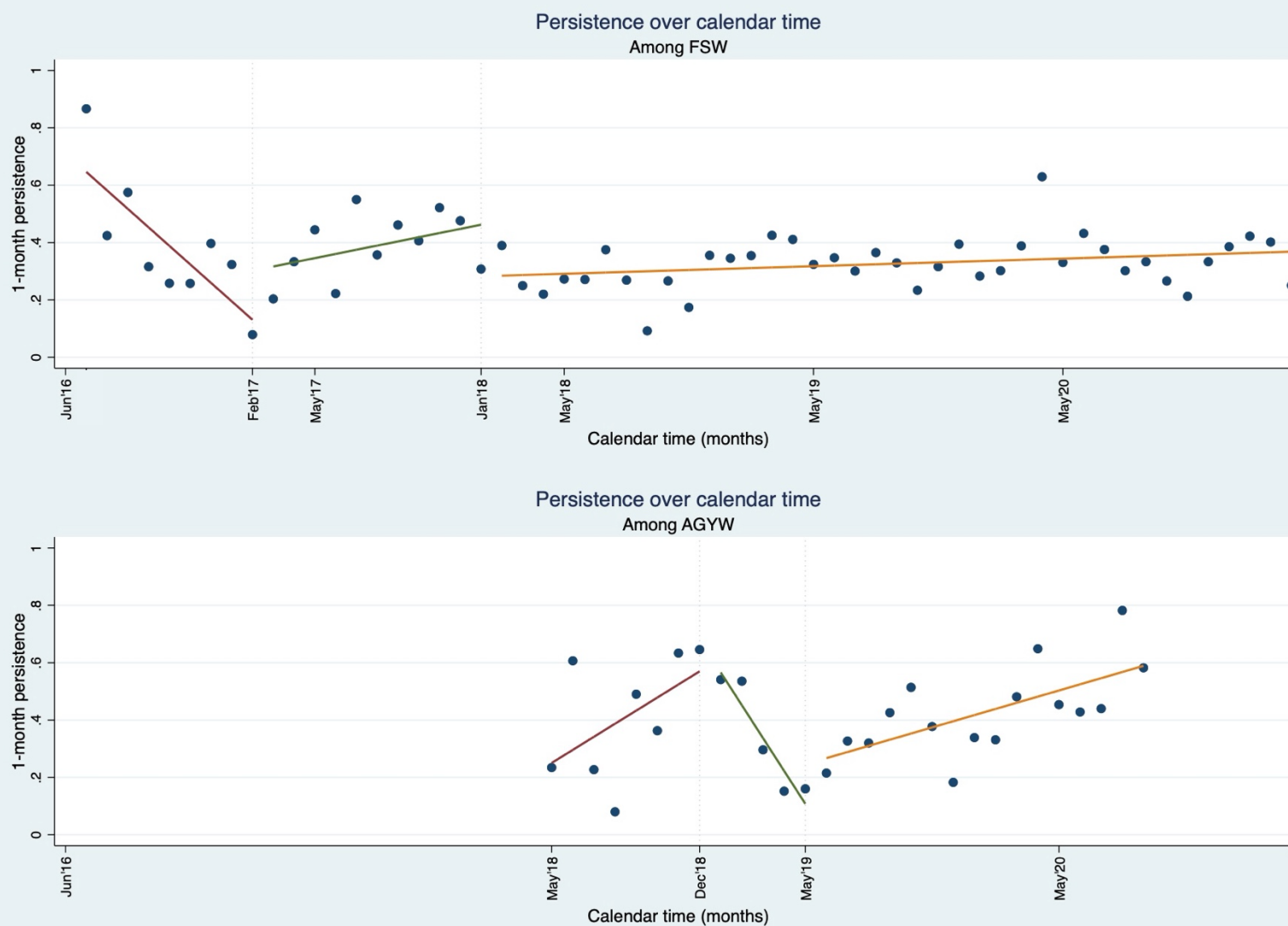
Chapter 4, Table 1. Implementation strategies utilized by TB HIV Care to improve PrEP persistence and the specific sites that adopted strategies between June 2016 and August 2021

Strategy	Implemented by the FSW program?	SITES	Implemented by the AGYW program?	SITES
Clinical mentoring for providers	Yes	uMgungundlovu OR Tambo	Yes	eThekwini uMgungundlovu Zululand uThukela Ekurhuleni OR Tambo Cape Town
Mobile van PrEP provision	Yes	eThekwini uMgungundlovu Ehlanzeni Gert Sibande Nkangala Kenneth Kaunda Ngaka Modiri Molema OR Tambo Cape Town	Yes	eThekwini uMgungundlovu Zululand uThukela Ekurhuleni OR Tambo Cape Town
SMS PrEP refill reminders	Yes	eThekwini uMgungundlovu Ehlanzeni Gert Sibande Nkangala Kenneth Kaunda Ngaka Modiri Molema OR Tambo Cape Town	Yes	eThekwini uMgungundlovu Zululand uThukela OR Tambo
SMS support texts	Yes	eThekwini uMgungundlovu Ehlanzeni Gert Sibande Nkangala Kenneth Kaunda Ngaka Modiri Molema OR Tambo Cape Town	Yes	eThekwini uMgungundlovu Zululand uThukela Ekurhuleni OR Tambo Cape Town
WhatsApp support groups	No		Yes	uMgungundlovu Zululand uThukela OR Tambo

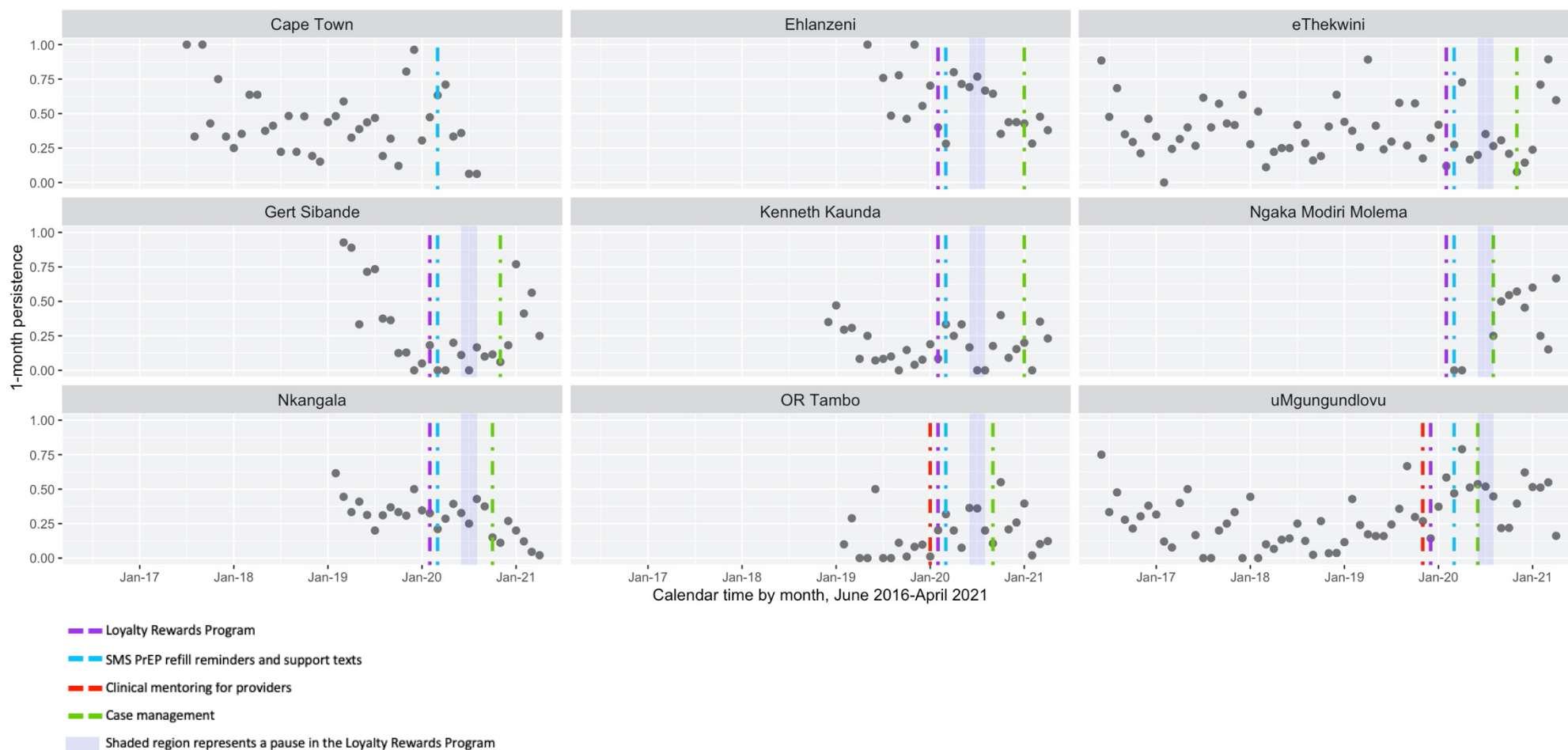
Case Management	Yes	eThekwini uMgungundlovu Ehlanzeni Gert Sibande Nkangala Kenneth Kaunda Ngaka Modiri Molema OR Tambo	Yes	eThekwini uMgungundlovu Zululand uThukela OR Tambo Cape Town
Loyalty rewards program	Yes	eThekwini uMgungundlovu Ehlanzeni Gert Sibande Nkangala Kenneth Kaunda Ngaka Modiri Molema OR Tambo	No	

Orange=KwaZulu-Natal province, Blue=Mpumalanga province, Gray=North West province,
Green=Eastern Cape province, Pink=Western Cape province, Black=Gauteng province

Chapter 4, Figure 2. 1-month PrEP persistence (number persisting/total initiated in the prior month) over calendar time among female sex workers and adolescent girls and young women receiving PrEP from TB HIV Care



Chapter 4, Figure 3. Monthly trends in the 1-month PrEP persistence (number persisting/total initiated in the prior month) by site implementing PrEP as part of the TB HIV Care program for female sex workers visualized against the introduction of several implementation strategies designed to promote PrEP persistence



Chapter 4, Table 2. Model results from a primary analysis of the impact of several implementation strategies on the 1-month persistence among female sex workers initiating PrEP through TB HIV Care and three secondary analyses

	PRIMARY Analysis	SECONDARY Analyses		
	1-month persistence	+ adjusting for total number eligible for PrEP	Removal of first introduction of loyalty rewards program	4-month persistence
Baseline persistence	0.37 (0.32, 0.42)	0.35 (0.30, 0.40)	0.37 (0.32, 0.43)	0.16 (0.13, 0.20)
β_1 (Calendar time)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (0.99, 1.01)
β_2 (SMS support)	1.33 (1.18, 1.50)	1.32 (1.18, 1.49)	1.26 (1.12, 1.40)	0.87 (0.73, 1.03)
β_3 (Case management)	1.02 (0.92, 1.13)	1.01 (0.91, 1.12)	1.16 (1.02, 1.32)	0.98 (0.84, 0.99)
β_4 (Loyalty rewards)	0.74 (0.67, 0.82)	0.75 (0.68, 0.84)	0.73 (0.64, 0.83)	0.84 (0.72, 0.97)
β_5 (Clinical mentoring)	1.12 (1.03, 1.23)	1.13 (1.03, 1.23)	1.04 (1.01, 1.13)	0.87 (0.75, 1.00)
β_6 (COVID-19 cases)	0.99 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

Chapter 4, Appendix Table 1. Implementation Strategies designed to promote PrEP persistence implemented by TB HIV Care

Strategy	Implementation details
Clinical mentoring for providers	Weekly: nurse clinicians or clinical trainers lead meetings to discuss best practices for PrEP provision among PrEP providers.
Mobile van PrEP provision	Daily: nurse clinicians and outreach workers take the TB HIV Care mobile van out into the community to provide decentralized PrEP.
SMS PrEP refill reminders	One week before and one day before scheduled refill: the program management team develops and sends automated text messages to remind PrEP users of a scheduled refill.
SMS support texts	Weekly: the program management team develops and sends out generic text messages of support designed to empower and promote self-efficacy.
WhatsApp support groups	On-demand: Nurse clinicians manage groups of PrEP users where members can discuss successes and challenges in using PrEP.
Case management approach	Weekly: Nurse clinicians and dedicated case managers are assigned to provide dedicated follow-up of PrEP users to provide support and guidance with regard to HIV prevention care.
Loyalty Rewards Program	Monthly: the program management team provides incentives in the form of airtime provided to individuals at initiation and upon returning for subsequent PrEP visits

Chapter 4, Appendix Table 2. Timing of TB HIV Care implementation strategy roll-out, availability of pre-strategy and post-strategy data, and decision about whether or not to include data in final interrupted time-series model

Pop	Site	Strategy	PrEP Start Date	Strategy start date	Number of pre-strategy months	Number of post-strategy months	End of study period	DECISION
FSW	eThekwini	Clinical mentoring for providers	Jun-16	NA			Jul-21	included, control
FSW	uMgungundlovu	Clinical mentoring for providers	Jun-16	Nov-19	41	20	Jul-21	included
FSW	Ehlanzeni	Clinical mentoring for providers	Sep-16	NA			Jul-21	included, control
FSW	Gert Sibande	Clinical mentoring for providers	Mar-19	NA			Jul-21	included, control
FSW	Nkangala	Clinical mentoring for providers	Feb-19	NA			Jul-21	included, control
FSW	Kenneth Kaunda	Clinical mentoring for providers	Dec-18	NA			Jul-21	included, control
FSW	Ngaka Modiri Molema	Clinical mentoring for providers	Mar-20	NA			Jul-21	included, control
FSW	OR Tambo	Clinical mentoring for providers	Feb-19	Jan-20	11	18	Jul-21	included
FSW	Cape Town	Clinical mentoring for providers	Jul-17	NA			Sep-20	included, control
FSW	eThekwini	Mobile van PrEP provision	Jun-16	Jun-16	0	61	Jul-21	not included; no pre-strategy data
FSW	uMgungundlovu	Mobile van PrEP provision	Jun-16	Jun-16	0	61	Jul-21	not included; no pre-strategy data
FSW	Ehlanzeni	Mobile van PrEP provision	Sep-16	Sep-16	0	58	Jul-21	not included; no pre-strategy data
FSW	Gert Sibande	Mobile van PrEP provision	Mar-19	Mar-19	0	28	Jul-21	not included; no pre-strategy data
FSW	Nkangala	Mobile van PrEP provision	Feb-19	Feb-19	0	29	Jul-21	not included; no pre-strategy data
FSW	Kenneth Kaunda	Mobile van PrEP provision	Dec-18	Dec-18	0	31	Jul-21	not included; no pre-strategy data
FSW	Ngaka Modiri Molema	Mobile van PrEP provision	Mar-20	Mar-20	0	16	Jul-21	not included; no pre-strategy data

FSW	OR Tambo	Mobile van PrEP provision	Feb-19	Feb-19	0	29	Jul-21	not included; no pre-strategy data
FSW	Cape Town	Mobile van PrEP provision	Jul-17	Jul-17	0	38	Sep-20	not included; no pre-strategy data
FSW	eThekwini	SMS PrEP Refill Reminders	Jun-16	Mar-20	45	16	Jul-21	included, combined with support texts
FSW	uMgungundlovu	SMS PrEP Refill Reminders	Jun-16	Mar-20	45	16	Jul-21	included, combined with support texts
FSW	Ehlanzeni	SMS PrEP Refill Reminders	Sep-16	Mar-20	42	16	Jul-21	included, combined with support texts
FSW	Gert Sibande	SMS PrEP Refill Reminders	Mar-19	Mar-20	12	16	Jul-21	included, combined with support texts
FSW	Nkangala	SMS PrEP Refill Reminders	Feb-19	Mar-20	13	16	Jul-21	included, combined with support texts
FSW	Kenneth Kaunda	SMS PrEP Refill Reminders	Dec-18	Mar-20	15	16	Jul-21	included, combined with support texts
FSW	Ngaka Modiri Molema	SMS PrEP Refill Reminders	Mar-20	Mar-20	0	16	Jul-21	included, combined with support texts
FSW	OR Tambo	SMS PrEP Refill Reminders	Feb-19	Mar-20	13	16	Jul-21	included, combined with support texts
FSW	Cape Town	SMS PrEP Refill Reminders	Jul-17	Mar-20	32	6	Sep-20	included, combined with support texts
FSW	eThekwini	SMS Support Texts	Jun-16	Mar-20	45	16	Jul-21	included, combined with refill reminders
FSW	uMgungundlovu	SMS Support Texts	Jun-16	Mar-20	45	16	Jul-21	included, combined with refill reminders
FSW	Ehlanzeni	SMS Support Texts	Sep-16	Mar-20	42	16	Jul-21	included, combined with refill reminders
FSW	Gert Sibande	SMS Support Texts	Mar-19	Mar-20	12	16	Jul-21	included, combined with refill reminders
FSW	Nkangala	SMS Support Texts	Feb-19	Mar-20	13	16	Jul-21	included, combined with refill reminders
FSW	Kenneth Kaunda	SMS Support Texts	Dec-18	Mar-20	15	16	Jul-21	included, combined with refill reminders

FSW	Ngaka Modiri Molema	SMS Support Texts	Mar-20	Mar-20	0	16	Jul-21	included, combined with refill reminders
FSW	OR Tambo	SMS Support Texts	Feb-19	Mar-20	13	16	Jul-21	included, combined with refill reminders
FSW	Cape Town	SMS Support Texts	Jul-17	Mar-20	32	6	Sep-20	included, combined with refill reminders
FSW	eThekwini	WhatsApp Support Groups	Jun-16	NA			Jul-21	not included; never implemented
FSW	uMgungundlovu	WhatsApp Support Groups	Jun-16	NA			Jul-21	not included; never implemented
FSW	Ehlanzeni	WhatsApp Support Groups	Sep-16	NA			Jul-21	not included; never implemented
FSW	Gert Sibande	WhatsApp Support Groups	Mar-19	NA			Jul-21	not included; never implemented
FSW	Nkangala	WhatsApp Support Groups	Feb-19	NA			Jul-21	not included; never implemented
FSW	Kenneth Kaunda	WhatsApp Support Groups	Dec-18	NA			Jul-21	not included; never implemented
FSW	Ngaka Modiri Molema	WhatsApp Support Groups	Mar-20	NA			Jul-21	not included; never implemented
FSW	OR Tambo	WhatsApp Support Groups	Feb-19	NA			Jul-21	not included; never implemented
FSW	Cape Town	WhatsApp Support Groups	Jul-17	NA			Sep-20	not included; never implemented
FSW	eThekwini	Case Management	Jun-16	Nov-20	53	8	Jul-21	included
FSW	uMgungundlovu	Case Management	Jun-16	Jun-20	48	13	Jul-21	included
FSW	Ehlanzeni	Case Management	Sep-16	Jan-21	52	6	Jul-21	included
FSW	Gert Sibande	Case Management	Mar-19	Nov-20	20	8	Jul-21	included
FSW	Nkangala	Case Management	Feb-19	Nov-20	21	8	Jul-21	included
FSW	Kenneth Kaunda	Case Management	Dec-18	Jan-21	25	6	Jul-21	included
FSW	Ngaka Modiri Molema	Case Management	Mar-20	Aug-20	5	11	Jul-21	included
FSW	OR Tambo	Case Management	Feb-19	Sep-20	19	10	Jul-21	included

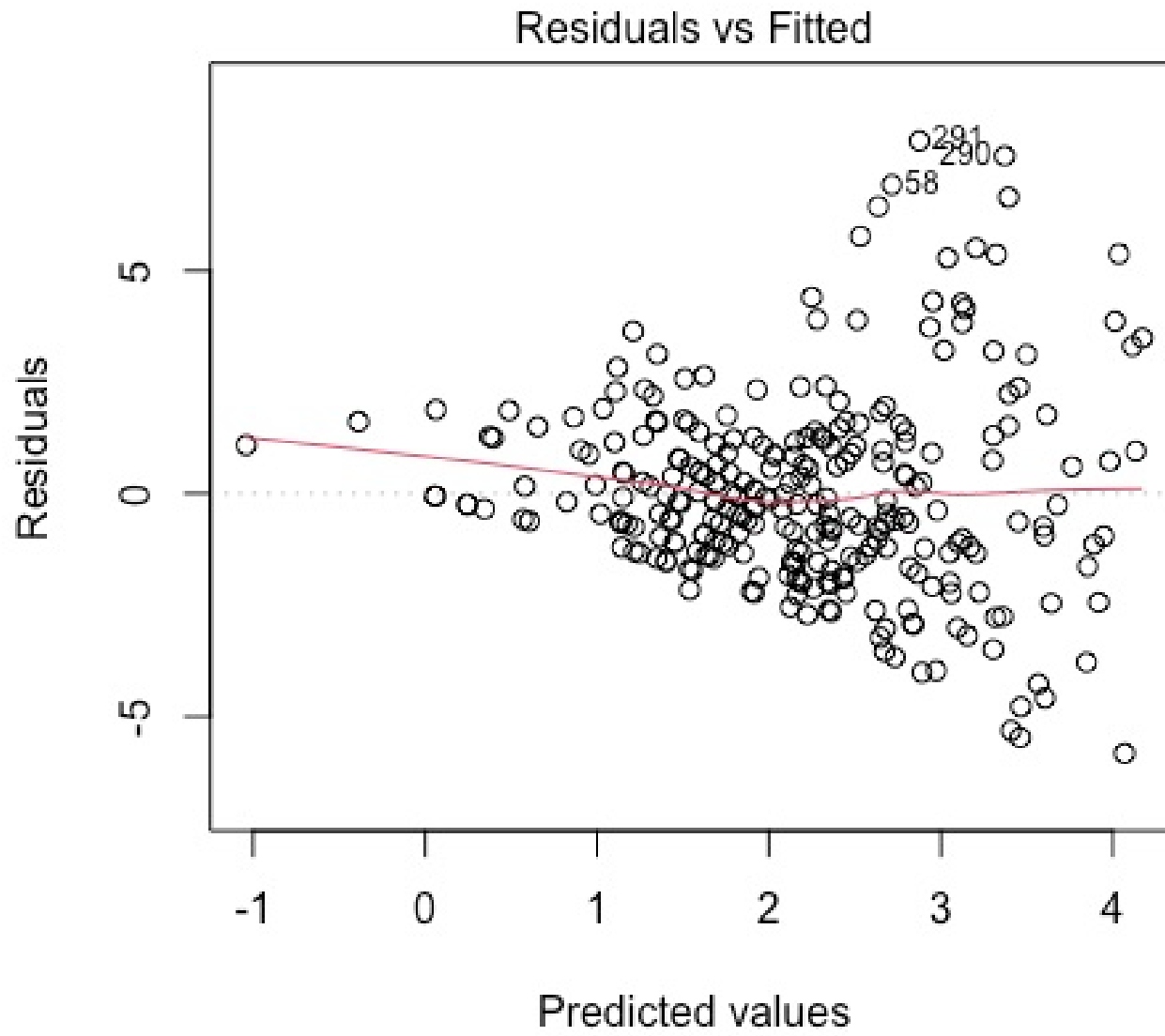
FSW	Cape Town	Case Management	Jul-17	NA			Sep-20	included, control
FSW	eThekwini	Loyalty Rewards Program	Jun-16	Feb-20	44	17	Jul-21	included, ABA design (temp stop date: June 2020, restart date: Aug 2020)
FSW	uMgungundlovu	Loyalty Rewards Program	Jun-16	Dec-19	42	19	Jul-21	included, ABA design (temp stop date: June 2020, restart date: Aug 2020)
FSW	Ehlanzeni	Loyalty Rewards Program	Sep-16	Feb-20	41	17	Jul-21	included, ABA design (temp stop date: June 2020, restart date: Aug 2020)
FSW	Gert Sibande	Loyalty Rewards Program	Mar-19	Feb-20	11	17	Jul-21	included, ABA design (temp stop date: June 2020, restart date: Aug 2020)
FSW	Nkangala	Loyalty Rewards Program	Feb-19	Feb-20	12	17	Jul-21	included, ABA design (temp stop date: June 2020, restart date: Aug 2020)
FSW	Kenneth Kaunda	Loyalty Rewards Program	Dec-18	Feb-20	14	17	Jul-21	included, ABA design (temp stop date: June 2020, restart date: Aug 2020)
FSW	Ngaka Modiri Molema	Loyalty Rewards Program	Mar-20	Mar-20	0	16	Jul-21	included, ABA design (temp stop date: June 2020, restart date: Aug 2020)
FSW	OR Tambo	Loyalty Rewards Program	Feb-19	Feb-20	12	17	Jul-21	included, ABA design (temp stop date: June 2020, restart date: Aug 2020)
FSW	Cape Town	Loyalty Rewards Program	Jul-17	NA			Sep-20	included, control
AGYW	eThekwini	Clinical mentoring for providers	Jan-20	Jan-20	0	18	Jul-21	not included; no pre-strategy data
AGYW	uMgungundlovu	Clinical mentoring for providers	May-18	May-18	0	38	Jul-21	not included; no pre-strategy data
AGYW	Zululand	Clinical mentoring for providers	Oct-20	Oct-20	0	9	Jul-21	not included; no pre-strategy data
AGYW	Uthukela	Clinical mentoring for providers	Oct-20	Oct-20	0	9	Jul-21	not included; no pre-strategy data

AGYW	Ekurhuleni	Clinical mentoring for providers	Oct-18	Oct-18	0	11	Sep-19	not included; no pre-strategy data
AGYW	OR Tambo	Clinical mentoring for providers	Oct-20	Oct-20	0	9	Jul-21	not included; no pre-strategy data
AGYW	Cape Town	Clinical mentoring for providers	Sep-18	Sep-18	0	34	Jul-21	not included; no pre-strategy data
AGYW	eThekwini	Mobile van PrEP provision	Jan-20	Jan-20	0	18	Jul-21	not included; no pre-strategy data
AGYW	uMgungundlovu	Mobile van PrEP provision	May-18	May-18	0	38	Jul-21	not included; no pre-strategy data
AGYW	Zululand	Mobile van PrEP provision	Oct-20	Oct-20	0	9	Jul-21	not included; no pre-strategy data
AGYW	Uthukela	Mobile van PrEP provision	Oct-20	Oct-20	0	9	Jul-21	not included; no pre-strategy data
AGYW	Ekurhuleni	Mobile van PrEP provision	Oct-18	Oct-18	0	11	Sep-19	not included; no pre-strategy data
AGYW	OR Tambo	Mobile van PrEP provision	Oct-20	Oct-20	0	9	Jul-21	not included; no pre-strategy data
AGYW	Cape Town	Mobile van PrEP provision	Sep-18	Sep-18	0	34	Jul-21	not included; no pre-strategy data
AGYW	eThekwini	SMS PrEP Refill Reminders	Jan-20	Aug-21	19		Jul-21	not included; implemented after the study period
AGYW	uMgungundlovu	SMS PrEP Refill Reminders	May-18	Oct-20	29	9	Jul-21	not included; implementation close to many other program changes (threats to validity)
AGYW	Zululand	SMS PrEP Refill Reminders	Oct-20	Sep-21	11		Jul-21	not included; implemented after the study period
AGYW	Uthukela	SMS PrEP Refill Reminders	Oct-20	Sep-21	11		Jul-21	not included; implemented after the study period
AGYW	Ekurhuleni	SMS PrEP Refill Reminders	Oct-18	NA			Sep-19	not included; control
AGYW	OR Tambo	SMS PrEP Refill Reminders	Oct-20	Sep-21	11		Jul-21	not included; implemented after the study period
AGYW	Cape Town	SMS PrEP Refill Reminders	Sep-18	NA			Jul-21	not included; control

AGYW	eThekwini	SMS Support Texts	Jan-20	Feb-20	1	17	Jul-21	not included; limited pre-strategy data
AGYW	uMgungundlovu	SMS Support Texts	May-18	Oct-20	29	9	Jul-21	not included; implementation close to many other program changes (threats to validity)
AGYW	Zululand	SMS Support Texts	Oct-20	Sep-21	11		Jul-21	not included; implemented after the study period
AGYW	Uthukela	SMS Support Texts	Oct-20	Sep-21	11		Jul-21	not included; implemented after the study period
AGYW	Ekurhuleni	SMS Support Texts	Oct-18	Oct-18	0	11	Sep-19	not included; no pre-strategy data
AGYW	OR Tambo	SMS Support Texts	Oct-20	Sep-21	11		Jul-21	not included; implemented after the study period
AGYW	Cape Town	SMS Support Texts	Sep-18	Sep-18	0	34	Jul-21	not included; no pre-strategy data
AGYW	eThekwini	WhatsApp Support Groups	Jan-20	NA			Jul-21	not included; control
AGYW	uMgungundlovu	WhatsApp Support Groups	May-18	Aug-20	27	11	Jul-21	not included; implementation close to many other program changes (threats to validity)
AGYW	Zululand	WhatsApp Support Groups	Oct-20	Sep-21	11		Jul-21	not included; implemented after the study period
AGYW	Uthukela	WhatsApp Support Groups	Oct-20	Sep-21	11		Jul-21	not included; implemented after the study period
AGYW	Ekurhuleni	WhatsApp Support Groups	Oct-18	NA			Sep-19	not included; control
AGYW	OR Tambo	WhatsApp Support Groups	Oct-20	Sep-21	11		Jul-21	not included; implemented after the study period
AGYW	Cape Town	WhatsApp Support Groups	Sep-18	NA			Jul-21	not included; control
AGYW	eThekwini	Case Management	Jan-20	Jan-21	12	11	Jul-21	not included; implementation close to many other program changes (threats to validity)

AGYW	uMgungundlovu	Case Management	May-18	Oct-20	29	9	Jul-21	not included; implementation close to many other program changes (threats to validity)
AGYW	Zululand	Case Management	Oct-20	Jun-21	8	1	Jul-21	not included; limited post-strategy data
AGYW	Uthukela	Case Management	Oct-20	Sep-21	11		Jul-21	not included; implemented after the study period
AGYW	Ekurhuleni	Case Management	Oct-18	NA			Sep-19	not included; control
AGYW	OR Tambo	Case Management	Oct-20	Jun-21	8	1	Jul-21	not included; limited post-strategy data
AGYW	Cape Town	Case Management	Sep-18	NA			Jul-21	not included

Chapter 4, Appendix Figure 1. Residuals plotted against predicted values from Poisson regression model examining implementation strategies among female sex workers



REFERENCES

1. Birdthistle I, Tanton C, Tomita A, et al. Recent levels and trends in HIV incidence rates among adolescent girls and young women in ten high-prevalence African countries: a systematic review and meta-analysis. *Lancet Glob Health* 2019; **7**(11): e1521-e40.
2. Naicker N, Kharsany AB, Werner L, et al. Risk Factors for HIV Acquisition in High Risk Women in a Generalised Epidemic Setting. *AIDS Behav* 2015; **19**(7): 1305-16.
3. Shisana O, Rehle T, Simbayi LC, et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town, 2014.
4. Birdthistle I, Kwaro D, Shahmanesh M, et al. Evaluating the impact of DREAMS on HIV incidence among adolescent girls and young women: A population-based cohort study in Kenya and South Africa. *PLoS Med* 2021; **18**(10): e1003837.
5. Buchbinder SP. Maximizing the Benefits of HIV Preexposure Prophylaxis. *Top Antivir Med* 2018; **25**(4): 138-42.
6. Braksmajer A, Senn TE, McMahon J. The Potential of Pre-Exposure Prophylaxis for Women in Violent Relationships. *AIDS Patient Care STDS* 2016; **30**(6): 274-81.
7. Thomson KA, Baeten JM, Mugo NR, Bekker LG, Celum CL, Heffron R. Tenofovir-based oral preexposure prophylaxis prevents HIV infection among women. *Curr Opin HIV AIDS* 2016; **11**(1): 18-26.
8. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363**(27): 2587-99.
9. South African National Department of Health. Guidelines for the Provision of Pre-exposure Prophylaxis (PrEP) to Persons at Substantial Risk of HIV Infection, 2020.
10. Pinto RM, Berringer KR, Melendez R, Mmeje O. Improving PrEP Implementation Through Multilevel Interventions: A Synthesis of the Literature. *AIDS Behav* 2018; **22**(11): 3681-91.
11. Underhill K, Guthrie KM, Collieran C, Calabrese SK, Operario D, Mayer KH. Temporal Fluctuations in Behavior, Perceived HIV Risk, and Willingness to Use Pre-Exposure Prophylaxis (PrEP). *Arch Sex Behav* 2018; **47**(7): 2109-21.
12. Barnighausen K, Geldsetzer P, Matse S, et al. Qualitative accounts of PrEP discontinuation from the general population in Eswatini. *Cult Health Sex* 2021; **23**(9): 1198-214.
13. Goparaju L, Praschan NC, Warren-Jeanpiere L, Experton LS, Young MA, Kassaye S. Stigma, Partners, Providers and Costs: Potential Barriers to PrEP Uptake among US Women. *J AIDS Clin Res* 2017; **8**(9).

14. Kambutse I, Igiraneza G, Ogbuagu O. Perceptions of HIV transmission and pre-exposure prophylaxis among health care workers and community members in Rwanda. *PLoS One* 2018; **13**(11): e0207650.
15. TB HIV Care: About Us. . 2021. <https://tbhivcare.org/issue/what-we-do/>.
16. Ibeneme SC, Ndukwu SC, Myezwa H, et al. Effectiveness of mobile text reminder in improving adherence to medication, physical exercise, and quality of life in patients living with HIV: a systematic review. *BMC Infect Dis* 2021; **21**(1): 859.
17. Abiodun O, Ladi-Akinyemi B, Olu-Abiodun O, et al. A Single-Blind, Parallel Design RCT to Assess the Effectiveness of SMS Reminders in Improving ART Adherence Among Adolescents Living with HIV (STARTA Trial). *J Adolesc Health* 2021; **68**(4): 728-36.
18. Visser CA, Wolvaardt JE, Cameron D, Marincowitz GJO. Clinical mentoring to improve quality of care provided at three NIM-ART facilities: A mixed methods study. *Afr J Prim Health Care Fam Med* 2018; **10**(1): e1-e7.
19. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2017; **46**(1): 348-55.
20. Rao A, Mhlophe H, Comins C, et al. Persistence on oral pre-exposure prophylaxis (PrEP) among female sex workers in eThekweni, South Africa, 2016–2020. *PLoS One* 2022.
21. Dorward J, Khubone T, Gate K, et al. The impact of the COVID-19 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis. *Lancet HIV* 2021; **8**(3): e158-e65.
22. Mutyambizi C, Dunlop J, Maluleke C, et al. Effect of COVID-19 on HIV, tuberculosis, and prevention of mother-to-child transmission of HIV indicators in Mopani district, South Africa. *S Afr Med J* 2021; **111**(12): 1181-9.
23. NICD. COVID-19 Surveillance Reports. <https://www.nicd.ac.za/diseases-a-z-index/covid-19/surveillance-reports/>.
24. Goparaju L, Experton LS, Praschan NC, Warren-Jeanpiere L, Young MA, Kassaye S. Women want Pre-Exposure Prophylaxis but are Advised Against it by Their HIV-positive Counterparts. *J AIDS Clin Res* 2015; **6**(11): 1-10.
25. Mack N, Odhiambo J, Wong CM, Agot K. Barriers and facilitators to pre-exposure prophylaxis (PrEP) eligibility screening and ongoing HIV testing among target populations in Bondo and Rarieda, Kenya: results of a consultation with community stakeholders. *BMC Health Serv Res* 2014; **14**: 231.
26. Eakle R, Bourne A, Jarrett C, Stadler J, Larson H. Motivations and barriers to uptake and use of female-initiated, biomedical HIV prevention products in sub-Saharan Africa: an adapted meta-ethnography. *BMC Public Health* 2017; **17**(1): 968.
27. Pilgrim N, Jani N, Mathur S, et al. Provider perspectives on PrEP for adolescent girls and young women in Tanzania: The role of provider biases and quality of care. *PLoS One* 2018; **13**(4): e0196280.

28. Collier KL, Colarossi LG, Sanders K. Raising Awareness of Pre-Exposure Prophylaxis (PrEP) among Women in New York City: Community and Provider Perspectives. *J Health Commun* 2017; **22**(3): 183-9.
29. Mayer KH, Sullivan PS, Beyrer C. Silver bullets and structural impediments to HIV prevention. *Lancet HIV* 2019; **6**(11): e729-e32.
30. Mugwanya KK, Pintye J, Kinuthia J, et al. Integrating preexposure prophylaxis delivery in routine family planning clinics: A feasibility programmatic evaluation in Kenya. *PLoS Med* 2019; **16**(9): e1002885.
31. Giovenco D, Muessig KE, Horvitz C, et al. Adapting technology-based HIV prevention and care interventions for youth: lessons learned across five U.S. Adolescent Trials Network studies. *Mhealth* 2021; **7**: 21.
32. Eakle R, Gomez GB, Naicker N, et al. HIV pre-exposure prophylaxis and early antiretroviral treatment among female sex workers in South Africa: Results from a prospective observational demonstration project. *PLoS Med* 2017; **14**(11): e1002444.
33. Gill K, Pidwell T, Dietrich J, et al. A Demonstration Open Label Study to Assess the Acceptability, Safety and Use of Truvada Pre-exposure Prophylaxis in Healthy, HIV-Uninfected Adolescents, 15-19 Years of Age. Conference of the International AIDS Society. Paris, France; 2017.
34. Machado DM, de Sant'Anna Carvalho AM, Riera R. Adolescent pre-exposure prophylaxis for HIV prevention: current perspectives. *Adolesc Health Med Ther* 2017; **8**: 137-48.
35. Gomez GB, Eakle R, Mbogua J, Akpomiemie G, Venter WD, Rees H. Treatment And Prevention for female Sex workers in South Africa: protocol for the TAPS Demonstration Project. *BMJ Open* 2016; **6**(9): e011595.
36. Haberer JE, Bukusi EA, Mugo NR, et al. Effect of SMS reminders on PrEP adherence in young Kenyan women (MPYA study): a randomised controlled trial. *Lancet HIV* 2021; **8**(3): e130-e7.
37. Shadish WR, Cook TD, Campbell DT. Experimental and Quasi-Experimental Designs for Generalized Causal Inference: Houghton, Mifflin and Company; 2002.
38. Westreich D, Edwards JK, Lesko CR, Cole SR, Stuart EA. Target Validity and the Hierarchy of Study Designs. *Am J Epidemiol* 2019; **188**(2): 438-43.

CHAPTER 5: CONCLUSIONS

Synthesis of Results

In this HIV prevention program serving adolescent girls and young women and female sex workers, we found that levels of PrEP initiation were comparable with what has been documented elsewhere in real-world program settings and that initiations continued to rise throughout the life of the program. We found that persistence on PrEP was poor, with more than half discontinuing after the first month, and that these outcomes were even worse for the youngest beneficiaries. We observed that persistence among those initiating in later years of the program, when the program had had more time to become established, was improved compared to those initiating earlier on. This was true even with an expanding number of young women served and an increased number of sites and staff to accommodate the growing demand and work. We learned that cycling on and off PrEP was common, with about 43% of female sex workers and 34% of adolescent girls and young women experiencing some form of cycling during the year following their initial PrEP initiation event. We also learned that SMS support and refill reminders and training for providers had a positive impact on 1-month persistence among female sex workers. Despite this observed association, however, these strategies alone were not enough to have a program-relevant impact on 1-month persistence, with persistence remaining low even after the introduction of these strategies.

Directions for Future Research

There are three key directions for future research. First, it will be important to understand *who* is at greatest risk of early discontinuation of PrEP, re-initiation, and the characteristics of those that are most likely to belong to the different identified latent trajectory groups. While we had individual-level data on age and year of initiation, the program data that we had access to and were able to successfully link with outcome data did not have information on additional demographic, clinical, and behavioral data. Future research could work to understand differences in PrEP outcomes by these different factors. It would also be useful to compare PrEP outcomes by program resources and characteristics, such as the level of resources available at a specific site in which a woman initiates, how she receives her PrEP, e.g. mobile van clinic or in-person clinic, and staff to patient ratios.

Second, further research is needed to understand reasons for discontinuation and re-initiation. As has been discussed in this dissertation, PrEP unlike treatment can depend on changing risks, and discontinuation may be intentional and not necessarily represent a negative outcome. For the over half of FSW and AGYW who never return after initiating, changing risk is likely not the driving factor behind their early drop-off from PrEP use, but for those who persist beyond 1-month and even experience cycling, further research is needed to understand reasons for these patterns of use. While much of the existing work in this area has been qualitative in nature, “need” for PrEP could also be assigned quantitatively using risk scores. We could then work to understand if discontinuation and cycling are related to changing patterns of risk or due to inadequate

availability and access to PrEP. The advantage of a quantitative risk assignment to bolster the qualitative literature on this subject would be that this could be done with a much larger sample of women.

Finally, as noted, we were unable to study the impact of different implementation strategies among adolescent girls and young women, and further research is needed to understand whether the same strategies that appeared beneficial for female sex workers would also be beneficial to adolescent girls and young women. It would also be important to test these same strategies using different methodologic approaches to further test the assumptions of our quasi-experimental study design.

Public Health Impact

In this dissertation, we described longitudinal patterns of PrEP use in one of the largest real-world cohorts of PrEP users in sub-Saharan Africa and identified key implementation strategies that may improve PrEP persistence. Given the incredibly high HIV incidence in this population, PrEP is an important tool for curtailing its spread. Better understanding patterns of PrEP use over time, particularly the cyclical nature of PrEP use, and the best strategies to increase persistence has the potential to optimize PrEP use and reduce new HIV acquisition events. We are beginning to understand that the youngest women, who have the highest risk of acquiring HIV, may also be the ones in greatest need of persistence support. The real-world implementation of PrEP is subject to changing donor priorities and constraints on resources and affecting real change in promoting PrEP use will necessitate providing implementing partners and program staff with sufficient support to meet growing patient demand.

The use of routine data poses many challenges but also offers many opportunities. Though routine data may be incomplete and organized in a way that is more suitable to clinical management and program-driven processes than research, these routine sources provide an opportunity to utilize data generated in a real-world setting. These data are often already collected and therefore do not create additional burden on program staff or additional expenditure on data collection. Programmatic data can also facilitate the study of much larger groups of people and can serve to answer questions that would otherwise be unanswerable. As the clinical management of PrEP users and other HIV prevention services further transitions to electronic health records in South Africa and elsewhere in sub-Saharan Africa, the opportunities for the use of routine data will only increase.

CURRICULUM VITAE

AMRITA RAO, ScM

PROFESSIONAL DATA

615 N. Wolfe Street, Baltimore MD 21205, E6534

arao24@jhu.edu

She/her/hers

EDUCATION AND TRAINING

PhD/2022 (expected)	Epidemiology, Johns Hopkins Bloomberg School of Public Health
ScM/2016	Epidemiology, Johns Hopkins Bloomberg School of Public Health
BS/2014	Human Biology, Health, and Society, Cornell University

PROFESSIONAL EXPERIENCE

Johns Hopkins University

Graduate Research Assistant, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2019-2022

Senior Research Program Coordinator, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2016-2019

Graduate Research Assistant, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2015-2016

Other Non-JHU Professional Experience

Research Intern, Tata Cornell Agriculture and Nutrition Initiative, Applied Economics and Management, Cornell University, 05/2014-08/2014

Research Intern, Center for Health Policy and Inequalities Research, Global Health Institute, Duke University, 05/2013-08/2013

Research Assistant, Laboratory for Rational Decision-Making, College of Human Ecology, Cornell University, 2012-2014

PROFESSIONAL ACTIVITIES

Scholarship Reviewer, International AIDS Society, 2019-2022

Member, Society for Epidemiologic Research, 2019-

Member, International AIDS Society, 2016-

EDITORIAL AND OTHER PEER REVIEW ACTIVITIES

Reviewer, American Journal of Epidemiology, 2021-

Reviewer, Prevention Science, 2021-

Reviewer, F1000 Research, 2021-

Reviewer, Annals of LGBTQ Public and Population Health, 2020-

Reviewer, SAHARA-J: Journal of Social Aspects of HIV/AIDS, 2020-

Reviewer, Annals of Epidemiology, 2020-

Reviewer, Archives of Sexual Behavior, 2019-

Reviewer, Systematic Reviews, 2019-

Reviewer, International Journal of STD & AIDS, 2018-

Reviewer, BMJ Open, 2017-

Reviewer, AIDS & Behavior, 2017-

Reviewer, Sexually Transmitted Infections, 2016-

Reviewer, Obstetrics & Gynecology, 2016-

HONORS AND AWARDS

Marilyn Menkes Book Award, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2021

Leon Gordis Centennial Scholarship: Excellence in Teaching, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2021

Global Health Field Research Award, Center for Global Health, Johns Hopkins Bloomberg School of Public Health, 2020

Inter-CFAR Implementation Science Fellow, Center for AIDS Research, Multiple Institutions, 2019

Mary B. Meyer Memorial Fund Scholar, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2019-2021

Global Health Established Field Placement, Center for Global Health, Johns Hopkins Bloomberg School of Public Health, 2015

Field Research Awardee, Tata-Cornell Agriculture Nutrition Initiative, Cornell University, 2014

Outstanding Senior Nominee, College of Human Ecology, Cornell University, 2014

Dean's List, College of Human Ecology, Cornell University 2011-2014

PUBLICATIONS

** indicates a mentored student or post-doctoral fellow*

Journal Articles

1. **Rao, A**, Mhlophe, H, Comins, C, Mcingana, M, Lesko, C, Mulumba, N, Baral, S, Hausler, H, Schwartz, S. Persistence on oral pre-exposure prophylaxis (PrEP) among female sex workers in eThekweni, South Africa, 2016-2020 PLoS One. 2022; 17(3): e0265434.
2. Redd AD, Peetluk LS, Jarrett BA, Hanrahan C, Schwartz S, **Rao A**, Jaffe AE, Peer AD, Jones CB, Lutz CS, McKee CD, Patel EU, Rosen JG, Garrison Desany H, McKay HS, Muschelli J, Andersen KM, Link MA, Wada N, Baral P, Young R, Boon D, Grabowski MK, Gurkey ES; Novel Coronavirus Research Compendium Team. Curating the evidence about COVID-19 for frontline public health and clinical care: the Novel Coronavirus Research Compendium. Public Health Rep. 2021.
3. **Rao A**, Schwartz S, Viswasam N, Rucinski K, Van Wickle K, Sabin K, Wheeler T, Zhao J, Baral S. Evaluating the quality of HIV epidemiologic evidence for populations in the absence of a reliable sampling frame: a modified quality assessment tool. Ann Epidemiol. 2021; S1047-2797(21)00219-2.
4. **Rao A**, Ma H, Moloney G, Kwong J, Juni P, Sander B, Kustra R, Baral S, Mishra S. A disproportionate epidemic: COVID-19 cases and deaths among essential workers in Toronto, Canada. Ann Epidemiol. 2021; 63: 63-67.
5. Stone, J, Mukandavire, C, Boily, MC, Fraser, H, Mishra, S, Schwartz, S, **Rao, A**, Looker, KL, Quaife, M, Terris-Prestholt F, Marr, A, Lane, T, Coetzee J, Gray G, Otway, K, Milovanovic, M, Hausler, H, Young, K, Mcingana, M, Ncendani, M, Puren, A, Hunt, G, Kose, Z, Phaswana-Mafuya, N, Baral, S, Vickerman, P. Estimating the contribution of key populations towards HIV transmission in South Africa. J Int AIDS Soc. 2021; 24(1): e25650.
6. Baral, S, Rucinski, K, Twahirwa Rwema JO, **Rao, A**, Diouf, D, Kamarulzaman, A, Phaswana-Mafuya, N, Mishra, S. The relationship between the global burden of influenza from 2017-2019 and COVID-19: a descriptive epidemiological assessment. JMIR Public Health Surveill. 2021; 7(3): e24696.
7. Rossouw, J, Schwartz, S, **Rao, A**, Mcingana, M, Young, K, Hausler, H, Baral, S. Exploring the association between depression and social and bio-behavioural HIV risk factors among female sex workers in Nelson Mandela Bay Municipality, South Africa. AIDS Red Hum

Retroviruses. 2021; 37(9): 666-675.

8. **Rao, A**, Rucinski, K, Jarrett, B, Ackerman, B, Wallach, S, Marcus, J, Adamson, T, Garner, A, Santos, GM, Beyrer, C, Howell, S, Baral, S. Perceived interruptions to HIV prevention and treatment services associated with COVID-19 for gay, bisexual, and other men who have sex with men in 20 countries. *J Acquir Immune Defic Syndr*. 2021; 87(1): 644-651.
9. Niu, XM, **Rao, A** (shared 1st), Chen, D, Sheng, B, Weir, S, Umar, E, Trapence, G, Jumbe, V, Kamba, D, Rucinski, K, Viswasam, N, Bao, L, Baral, S. Using factor analyses to estimate the number of female sex workers across Malawi from multiple regional sources. *Ann Epidemiol*. 2020; 55: 34-40.
10. Silhol, R, Baral, S, Bowring, AL, Mukandavire, C, Njindam, IM, **Rao, A**, Schwartz, S, Tamoufe, U, Billong, SC, Njoya, O, Bissek AC, Calleja JMG, Vickerman, P, Mishra, S, Boily, MC. Quantifying the evolving contribution of HIV interventions and key populations to the HIV epidemic in Yaoundé, Cameroon. *J Acquir Immune Defic Syndr*. 2020; 84(4): 396-405.
11. Datta A, Pita A, **Rao, A**, Sithole, B, Mnisi Z, Baral, S. Size estimation of key populations in the HIV epidemic in eSwatini using incomplete and misaligned capture-recapture data. *Ann Appl Stat*. 2020. 14(3): 1207-1241.
12. Zhao, Y*, **Rao, A**, Wirtz, AL, Umar, E, Trapence, G, Jumbe, V, Ketende, S, Kamba, D, Beyrer, C, Baral, S. A structural equation model of factors associated with HIV risk behaviors and mental health among men who have sex with men in Malawi. *BMC Inf Dis*. 2020; 20(1): 591.
13. Santos GM, Ackerman B, **Rao A**, Wallach S, Ayala G, Lamontage E, Garner, A, Holloway, I, Arreola, S, Silenzio, V, Stromdahl, S, Yu, L, Strong, C, Adamson, T, Yakusik A, Doan, TT, Huang, P, Cerasuolo, D, Bishop, A, Noori, T, Pharris, A, Aung, M, Dara, M, Chung, SY, Hanley, M, Baral, C, Howell, S. Economic, Mental Health, HIV Prevention and HIV Treatment Impacts of COVID-19 and the COVID-19 Response on a Global Sample of Cisgender Gay Men and Other Men Who Have Sex with Men. *AIDS Behav*. 2020; 25(2): 311-321.
14. Bowring AL, Schwartz S, Lyons C, **Rao A**, Olawore O, Njindam IM, Nzau, J, Fouda, G, Fako, GH, Turpin, G, Levitt, D, Georges, S, Tamoufe, U, Billong, SC, Njoya, O, Zoung-Kanyi, AC, Baral, S. Unmet Need for Family Planning and Experience of Unintended Pregnancy Among Female Sex Workers in Urban Cameroon: Results From a National Cross-Sectional Study. *Glob Health Sci Pract*. 2020;8(1):82-99.
15. Moazzami M, Ketende S, Lyons C, **Rao A**, Taruberekera N, Nkonyana J, Mothopeng, T, Schwartz, S, Baral, S. Characterizing Multi-level Determinants of HIV Prevalence Among Female Sex Workers in Maseru and Maputsoe, Lesotho. *AIDS Behav*. 2020;24(3):714-23.

16. Viswasam N, Lyons CE, MacAllister J, Millett G, Sherwood J, **Rao A**, et al. The uptake of population size estimation studies for key populations in guiding HIV responses on the African continent. *PLoS One*. 2020;15(2):e0228634.
17. Smith, JD, Li, DH., Hirschhorn, LR, Gallo, C, McNulty, M, Phillips, G, Birkett, M, Rafferty, M. **Rao, A**, Villamar, JA, Baral, S, Mustanski, B, Brown, CH., Benbow, ND. Landscape of HIV Implementation Research Funded by the National Institutes of Health: A Mapping Review of Project Abstracts. *AIDS Behav*. 2020;24(6):1903-11.
18. Schwartz SR, **Rao A**, Rucinski KB, Lyons C, Viswasam N, Comins CA, Olawore, O, Baral, S. HIV-Related Implementation Research for Key Populations: Designing for Individuals, Evaluating Across Populations, and Integrating Context. *J Acquir Immune Defic Syndr*. 2019;82 Suppl 3:S206-S16.
19. Ouedraogo HG, Zida S, Compaore TR, Lanou BH, **Rao A**, Sagna T, Kadari, C, Tarnagda, G, Ky-Zerbo, O, Traore, Y, Baral, S, Kouanda, S, Barro, N. Seroepidemiology of syphilis among men who have sex with men in Burkina Faso, West Africa. *Eur J Clin Microbiol Infect Dis*. 2019;38(10):1803-9.
20. Baral S, **Rao A**, Sullivan P, Phaswana-Mafuya N, Diouf D, Millett G, Musyoki, H, Geng, E, Mishra, S. The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment. *Lancet HIV*. 2019;6(9):e632-e8.
21. Parmley L*, **Rao A**, Young K, Kose Z, Phaswana-Mafuya N, Mcingana M, Lambert, A, Hausler, H, Baral, S, Schwartz, S. Female Sex Workers' Experiences Selling Sex during Pregnancy and Post-Delivery in South Africa. *Stud Fam Plann*. 2019;50(3):201-17.
22. **Rao A**, Ewing W, Ketende S, Wirtz AL, Jumbe V, Trapence G, Kamba, D, Umar, E, Muula, AS, Baral, S. Correlates of Water-Based Lubricant Use Among Men Who Have Sex with Men in Blantyre, Malawi. *AIDS Res Hum Retroviruses*. 2019;35(9):833-41.
23. Srivatsan, V*, Schwartz, S, **Rao, A**, Rolfe, J, Mpooa, N, Mothopeng, T, Nkonyana, J, Baral, S. Engagement in Antiretroviral Treatment and Modern Contraceptive Methods Among Female Sex Workers Living With HIV in Lesotho, *Women's Reproductive Health*, 2019; 6:3, 204-221.
24. Bowring AL, Ketende S, **Rao A**, Mfochive Njindam I, Decker MR, Lyons C, Levitt, D, Olawore, O, Turpin, G, Fako, GH, Fouda, G, Tamoufe, U, Billong, SC, Njoya, O, Bissek, AC, Baral, S. Characterising unmet HIV prevention and treatment needs among young female sex workers and young men who have sex with men in Cameroon: a cross-sectional analysis. *Lancet Child Adolesc Health*. 2019;3(7):482-91.
25. Parmley L*, **Rao A**, Kose Z, Lambert A, Max R, Phaswana-Mafuya N, Mcingana, M, Hausler, H, Baral, S, Schwartz, S. Antenatal care presentation and engagement in the context of sex work: exploring barriers to care for sex worker mothers in South Africa. *Reprod Health*. 2019;16(Suppl 1):63.

26. **Rao A**, Schwartz S, Billong SC, Bowring A, Fouda G, Ndonko F, Njindam, I, Levitt, D, Bissek, AC, Njoya, O, Baral, S. Predictors of early childhood HIV testing among children of sex workers living with HIV in Cameroon. *BMC Public Health*. 2019;19(Suppl 1):602.
27. Twahirwa Rwema JO, Baral S, Ketende S, Phaswana-Mafuya N, Lambert A, Kose Z, Mcingana, M, **Rao, A**, Hausler, H, Schwartz, S. Evaluating the vertical HIV transmission risks among South African female sex workers; have we forgotten PMTCT in their HIV programming? *BMC Public Health*. 2019;19(Suppl 1):605.
28. Twahirwa Rwema JO, Lyons CE, Ketende S, Bowring AL, **Rao A**, Comins C, Diouf, D, Drame, FM, Liestman, B, Coly, K, Ndour, C, Turpin, G, Mboup, S, Toure-Kane, C, Castor, D, Leye-Diouf, N, Diop-Ndiaye, H, Baral, S. Characterizing the Influence of Structural Determinants of HIV Risk on Consistent Condom Use Among Female Sex Workers in Senegal. *J Acquir Immune Defic Syndr*. 2019;81(1):63-71.
29. Bowring AL, Ketende S, Billong SC, Mfochive Njindam I, **Rao A**, Decker MR, Lyons, C, Turpin, G, Fako, G, Olawore, O, Ndonko, F, Levitt, D, Fouda, G, Tamoufe, U, Njoya, O, Bissek AC, Baral, S. Characterizing Sociostructural Associations With New HIV Diagnoses Among Female Sex Workers in Cameroon. *J Acquir Immune Defic Syndr*. 2019;80(3):e64-e73.
30. Datta, A, Lin, W, **Rao, A**, Diaouf, D, Kouama, A, Edwards, JK, Bao, L, Louis, TA, Baral, S. Bayesian estimation of MSM population in Cote d'Ivoire. *Statistics and Public Policy*. 2018; 6(1): 1-13.
31. **Rao A**, Schwartz S, Sabin K, Wheeler T, Zhao J, Hargreaves J, Baral, S, Global.HIV Research Group. HIV-related data among key populations to inform evidence-based responses: protocol of a systematic review. *Syst Rev*. 2018;7(1):220.
32. Wells C, Schwartz S, Phaswana-Mafuya N, Lambert A, Kose Z, McIngana M, Hausler, H, **Rao, A**, Yah, C, Ketende, S, Baral, S. Characterizing the Patterns of HIV Disclosure to Clients Among South African Female Sex Workers in Port Elizabeth. *AIDS Behav*. 2018;22(12):3924-32.
33. **Rao A**, Stahlman S, Hargreaves, J, Weir, S, Edwards, J, Rice, B, Kochelani, D, Mavimbela, M, Baral, S. Sampling key populations for HIV surveillance: results from eight cross-sectional studies using respondent-driven sampling and venue-based snowball sampling. *JMIR Public Health Surveill*. 2017; 3(4): e72.
34. **Rao A**, Tobin K, Davey-Rothwell M, Latkin CA. Social Desirability Bias and Prevalence of Sexual HIV Risk Behaviors Among People Who Use Drugs in Baltimore, Maryland: Implications for Identifying Individuals Prone to Underreporting Sexual Risk Behaviors. *AIDS Behav*. 2017;21(7):2207-14.

35. **Rao A**, Baral S, Phaswana-Mafuya N, Lambert A, Kose Z, Masinga M, Holland, C, Ketende, S, Schwartz, S. Pregnancy Intentions and Safer Pregnancy Knowledge Among Female Sex Workers in Port Elizabeth, South Africa. *Obstet Gynecol.* 2016;128(1):15-21.

Chapters

1. Viswasam, N, Rivera, J, Comins, C, **Rao, A**, Lyons, C, Baral, S (2021). The epidemiology of HIV among sex workers around the world: implications for research, programmes, and policy (Chapter 2) In *Sex work, health, and human rights: global inequities, challenges, and opportunity for action*.

PRACTICE ACTIVITIES

Practice-Related Reports

1. **Rao, A**, Viswasam, N, Baral, S. Strengthening capacity for assessment of HIV-related data needs among key populations to inform evidence-based responses. Population Council. 2020. doi: 10.31899/hiv11.1007.

Presentations to Policymakers, Communities, and Other Stakeholders

1. Co-presenter. “Key Population Size Estimation Consultation, Initial Consultation” Project SOAR. Lusaka, Zambia. November 2019.
2. Co-presenter. “Consultation on conducting respondent-driven sampling as part of an integrated bio-behavioral survey with key populations” Project SOAR. Lilongwe, Malawi. December 2018.
3. Co-organizer. “Improving key population estimates in mathematical models characterizing the HIV epidemic in South Africa.” Project SOAR. Johannesburg, South Africa. November 2018.
4. Co-presenter. “HIV Key Populations Capacity Building Workshop” Project SOAR. Ezulwini, eSwatini. July 2018.
5. Co-presenter. “HIV Key Populations Capacity Building Workshop” Project SOAR. Blantyre, Malawi April 2018.

Media Dissemination

Traditional Media

1. Bernstein, L. When one pandemic disrupts another: COVID-19 transforms international AIDS Conference. *Washington Post*, July 2020.

Social Media, Podcasts, Blog Posts, Videos

1. “Impacts of COVID-19 on Global LGBTQ+ Communities and Those At-Risk of HIV.” Invited Panel Discussion (Virtual). Tech4HIV. July 2020.

PART II

TEACHING

Classroom Instruction – Teaching Assistant (Johns Hopkins Bloomberg School of Public Health)

PH.340.717: Health Survey Research Methods, 2019-2021

PH.340.727: Introduction to Health Survey Research Methods: Online, 2020-2021

PH.340.727: Introduction to Health Survey Research Methods: Summer Institute, 2019-2021

PH.340.726: Implementation Research Methods to Address Real World Epidemiological Questions, 2020-

PH.340.863: Doctoral Seminars in Epidemiology I & II, 2020

PH.410.606: Local and Global Best Practices in Health Equity Research Methods, 2020

PH.340.753: Epidemiologic Methods III, 2019

PH.340.752: Epidemiologic Methods II, 2015 & 2019

Classroom Instruction – Teaching Assistant (Cornell University)

NS 4500: Public Health Nutrition, 2014

NS 3220: Maternal and Child Nutrition, 2014

BIOG 1105: Introductory Biology, 2013

RESEARCH GRANT PARTICIPATON

PrEP among high-risk young women in South Africa: real-world patterns of re-initiation and PrEP cycling, 2020-2022, National Institutes of Mental Health

Grant No. F31MH124458

PI: **Rao**, \$91,556

HIV incidence is disproportionately high among adolescent girls and young women (AGYW) and young female sex workers (YFSW) in South Africa. Pre-exposure prophylaxis for HIV prevention (PrEP) promises to be an efficacious, female-controlled HIV prevention opportunity, but the little data that do exist in South Africa suggest implementation challenges: initiation remains low and many women discontinue use shortly after starting. This study will harness routinely-collected data from the largest PrEP provider in South

Africa to 1) describe initiation and retention trends of PrEP and identify characteristics of those unlikely to adopt PrEP and prone to drop-out of services, 2) explore patterns of PrEP re-initiation and cycling among those ever initiated, 3) develop methods, including in how to link records over time, to repurpose and make use of routinely collected HIV program data.

ACADEMIC SERVICE

Co-president, Epidemiology Student Organization, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2020-2021

Co-lead, Social Epidemiology Student Organization, Johns Hopkins Bloomberg School of Public Health, 2020-2022

Member, Epidemiology, Inclusion, Diversity, Equity, Anti-Racism, and Science (IDEAS), Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2019-2022

Master's Representative, Epidemiology Student Organization, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2015-2016

Coordinator, General Epidemiology and Methodology (GEM) Journal Club, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2015-2016

PRESENTATIONS

Scientific Meetings

“Persistence on oral pre-exposure prophylaxis (PrEP) among female sex workers in Durban, South Africa.” Poster presentation. IAS. July 2021. Virtual Conference.

“Global Interruptions in HIV prevention and treatment services as a result of the response to COVID-19: results from a social media-based sample of men who have sex with men.” Late-breaker Oral Abstract. AIDS. July 2020. Virtual Conference.

“Extrapolation of population size estimates for key populations: illustrating the effects of different extrapolation approaches on estimating the number.” Poster discussion. IAS. July 2019. Mexico City, Mexico.

“Unmet need for modern contraception: challenges reaching female sex workers without a prior pregnancy in Swaziland.” Poster presentation. AIDS. July 2018. Amsterdam, Netherlands.

“Importance of antenatal care attendance and mother’s awareness of status on early childhood HIV testing among female sex workers living with HIV in Cameroon.” Poster presentation. IAS. July 2017. Paris, France.

“Pregnancy intentions and safer pregnancy knowledge among female sex workers in Port Elizabeth, South Africa.” Oral abstract. AIDS. July 2016. Durban, South Africa.

Invited Seminars

“PrEP among young women at high-risk for HIV in South Africa: real-world barriers to use and strategies to improve retention.” Invited talk. CHIMERA Fellow Workshop. TREAT Asia. amfAR. December 2020. Virtual webinar.

“The Impact of COVID-19 on Key Populations.” Invited talk. Center for Global Health. June 2020. Virtual webinar.

“Perspectives on different sampling approaches.” Invited talk. Measurement & Surveillance of HIV Epidemics (MeSH) Consortium Scientific Symposium. December 2017. Muldersdrift, South Africa.

“Current Approaches for Extrapolation of Population Size Estimates.” Invited talk. Consultation on Estimating the Size of Key populations in Resource-Limited Settings, Centers for Disease Control and Prevention. January 2017. Atlanta, USA

ADDITIONAL INFORMATION

My research goals center on understanding and addressing the HIV prevention and treatment needs of marginalized populations, specifically female sex workers and adolescent girls and young women. I have a specific interest in studying and mitigating barriers to health related to social inequity, stigma, and discrimination. My work to date has used modern epidemiologic methods, including survival analysis in the context of competing risks, methods in implementation science, and more recently quasi-experimental causal inference approaches. I have led work which examines social desirability bias among people who use drugs in Baltimore City, assesses differences in non-probability sampling techniques for hidden populations, and identifies predictors of early childhood HIV testing among children of female sex workers. My current work and a primary direction for future work is in the use of routinely collected data and non-traditional data sources to inform service delivery and reduce disparities in access to healthcare.

Keywords

HIV; Women’s Health; Implementation Science; Health Equity