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Factors associated with pre-exposure prophylaxis (PrEP) uptake and continuation among adolescent girls and young women in the uMhlathuze Municipality, KwaZulu-Natal South Africa

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CANDIDATES DECLARATION

I, Jewelle Joanna Sardis Methazia, declare that this research report is my own work. It is being submitted in partial fulfilment of the requirements for the degree Master of Epidemiology (Epidemiology and Biostatistics) at the University of the Witwatersrand, Johannesburg. This report has not been submitted previously at this or any other University for any degree or examination.

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On the 13th day of June 2023

DEDICATION

I dedicate this report to my mother Ms. M Jandles and my partner Mr. M Krienke who have encouraged me and supported me throughout my academic endeavors. My family whose belief in me has kept me grounded and motivated; and to God who promises that I can do all things through him.

ABSTRACT

Background

Despite the notable advancements in preventing human immunodeficiency-virus (HIV) globally, South Africa (SA) continues to report the largest epidemic of HIV in the world. Furthermore, adolescent girls and young women AGYW) in SA carry the unequal burden of infection in SA. Studies have reported that AGYWs find it difficult to negotiate condom use placing them at a direct risk of contracting HIV. Pre-exposure prophylaxis (PrEP) was identified as a novel preventative intervention with uptake and continued use offering the potential to decrease HIV incidence. In SA, guidelines, and strategies to provide of PrEP to high-risk groups, which include AGYW have been developed. This study aimed to describe the characteristics of the AGYW initiating PrEP services and determine the factors associated with PrEP uptake and continued use among AGYW enrolled in an HIV prevention combination program in the uMhlathuze Municipality in KwaZulu-Natal South Africa.

Methods

This is a retrospective cohort study involving secondary data analysis of programmatic data from an HIV combination prevention program for AGYW in 5 Department of Health community primary health clinics the uMhlathuze Municipality in KwaZulu-Natal. We sampled participants from a population of HIV uninfected AGYW between the ages 15 -24 that initiated the program between the 1st of June 2020 and the 31st of June 2021. Our primary outcome of interest was PrEP initiation at baseline defined as the number of AGYW who were offered PrEP and initiate its use during at their first visit. Our secondary outcome of interest was PrEP continuation at follow-up visit defined as having at least 1 record of follow up after PrEP initiation.

Categorical variables were expressed as frequencies and proportions. Bivariable analysis was carried out to determine associations between PrEP initiation and the categorical variables using the Chi-squared ($\chi 2$) test. Log-binomial regression was utilised to evaluate risk factors associated with our primary outcome (PrEP initiation) and our secondary outcome (PrEP continuation). Risk ratios (RRs) and their 95% CI were used as the measure of effect. Variables with $p<0.1$ were included in the multivariable analysis for both PrEP initiation and PrEP continuation to ascertain factors associated with each outcome. A cut off $p<0.05$ was used in the multivariable model to identify factors associated with both the primary (PrEP initiation) and secondary outcome (PrEP continuation). All statistical analyses were performed using Stata (V.15) statistical software and RStudio.

Results

Between the 1st of June 2020 and the 31st of June 2021, 3324 AGYW were enrolled in the HIV prevention combination program and were offered PrEP services. Overall, 1609 (48%) initiated PrEP services. Majority (71%) were aged 19 - 24 and 6.5% of PrEP initiates reported having an STI in the 6 months prior to initiating PrEP pills. Among those that initiated PrEP only 8% (N=125) had at least 1 record of follow-up post initiation. Factors that remained significantly associated with PrEP initiation in the multivariable analysis were had STI in the last 6 months (RR:2, CI: 1.5-2.8, p<0.001); currently on STI treatment (RR:1.6, CI: 1.2-2.3, p=0.004); used condom at last sexual encounter (RR:1.8, CI: 1.2-2.8, p=0.007). For our secondary outcome of interest PrEP continuation, factors associated with continued use of PrEP in our univariable analysis were age category 19-24 (RR:0.7, CI:0.5-1.0, p=0.036); used condom at last sex (RR: 1.7, CI:0.9-3.2, p=0.092). However, none of these factors remained statistically significant predictors of PrEP continuation in the multivariable model.

Conclusion

This study had moderate uptake of PrEP and poorer continuation than other studies. It is possible that lockdown restrictions implemented to curb the transmission of COVID-19 at the time of the study may have hampered the success of the PrEP intervention for AGYW enrolled in the HIV combination prevention program. This finding calls for more innovative PrEP service delivery models for programs and interventions in real clinic settings to ensure AGYW have uninterrupted access to PrEP when access to clinics is restricted. Our findings demonstrate important differences between PrEP uptake and key sexual and HIV risk behaviours. Our unadjusted analysis showed positive associations between PrEP uptake and the use of condoms at last sexual encounter, current STI diagnosis and STI diagnosis in the last 6 months, pregnancy, HIV discordant relationships, and having heterosexual anal sex. We continued to observe positive associations between the PrEP uptake and the use of condoms at last sexual encounter, current STI diagnosis and STI diagnosis in the last 6 months in our adjusted analysis. Condom use at last sexual encounter was common among PrEP initiates, and many AGYW currently taking STI treatment and those who had an STI in the last 6 months also elected to use PrEP pills. Our findings indicate programs offering PrEP should also integrate STI services with appropriate testing approaches and targeted vaccination for AGYW.

Key words: *Oral pre-exposure prophylaxis, adolescent girls, young women, HIV prevention, sexually transmitted infections, COVID-19, South Africa*

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ABBREVIATIONS

AGYW	Adolescent Girls and Young Women
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral
FTC	emtricitabine
HIV	Human immunodeficiency-virus
KZN	KwaZulu -Natal
MSM	Men who have sex with men
NDoH	National Department of Health
PLWHIV	People Living with Human Immunodeficiency Virus
PrEP	Pre-exposure prophylaxis
SA	South Africa
SEM	Socio-ecological model
SRH	Sexual and reproductive health
STI	Sexually transmitted infection
TDF	tenofovir disoproxil fumarate
TFV-DP	Tenofovir diphosphate
WHO	World Health Organization
YWSS	Young women who sell sex

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1 CHAPTER 1: INTRODUCTION

This chapter explores the history of HIV in SA, its prevalence among adolescent girls and young women (AGYW), and the introduction of pre-exposure prophylaxis (PrEP) interventions in South Africa. This chapter appraises the existing evidence on the interplay of factors affecting the initiation and continued use of oral PrEP among AGYW in SA. This section will also explore these factors by fitting a conceptual framework and will discuss the challenges and the gaps in the existing literature. The section concludes with the rationale for this study and its specific aims and objectives.

1.1 Background

The virus known as Human immunodeficiency virus (HIV) attacks the immune system, it can lead to opportunistic infections and the disease acquired immunodeficiency syndrome (AIDS) (1). In South Africa (SA), the HIV epidemic is historically linked to the socio-political and economic evolution of South Africa (2). According to an early survey among mine workers, HIV was first detected in SA in 1982 and showed approximately 3% of foreign miner workers had HIV while prevalence was lower among South African mine workers (2). By the early 2000s HIV prevalence had risen among the population and AIDs accounted for 40% of deaths in adults. The prevalence of HIV continued to rapidly increase to 18.9% in people aged 15 to 49 in 2005 (3). More recently, despite the notable advancements in preventing globally, The HIV epidemic in SA continues to be the largest in the world. According to a 2021 report from Statistics South Africa (STATSSA) people living with HIV (PLHIV) account for 13.7% of the population (4).

In SA women withstand the worst of unequal burden of HIV infection and this disparity is distinctly higher among AGYWs. Biologically, AGYW are more susceptible to HIV infection

when there are damages to the protective mucosal linings of the female reproductive system (5). Young women are also more susceptible to acquiring HIV if their male partner is uncircumcised (6). Furthermore, their risk of HIV infection significantly increases during pregnancy (7). The World Health Organisation (2021) defines adolescents as the interval between ages 10 and 19, this time span also falls within the definition of young people which is categorised as ages 10 and 24 (8). In SA among AGYW aged 15 to 24 the prevalence of HIV is 4 times that of their male counterparts (9). The increased incidence of HIV among AGYW is driven by multiple factors involving an interplay of biological, socioeconomic, behavioural and structural issues (10,11). Studies conducted in SA have also reported AGYWs difficulty in negotiating condom use which places them at a direct risk of acquiring HIV , and that this is even more pronounced in intergenerational relationships (12). Poor uptake and inconsistent use of HIV prevention methods has stalled the eradication of HIV.

Efforts to prevent HIV have been centred around behaviour modification and biomedical strategies that interrupt transmission of HIV. Oral pre-exposure prophylaxis (PrEP) was identified as a novel intervention in HIV prevention and the potential of uptake and continued use to decrease new infections. It is an oral antiretroviral (ARV) medication, taken daily that is comprised of a mixture of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) (13). The WHO developed guidelines in 2015 that endorse oral PrEP as a HIV prevention intervention to be used in conjunction with other HIV prevention methods for persons at considerable risk (13). Evidence has demonstrated the potency of PrEP offering above 90% protection from HIV when used correctly (14). Early research to determine the efficacy of PrEP were conducted among men who have sex with men (MSM), finding PrEP to be efficacious in the prevention of HIV when adhered to in this population group (15) . However, other research has found PrEP efficacy to be lower among heterosexual users, ranging between

64% and 84% with the lower efficacy being subscribed to poor adherence among these users (16).

1.1.1 PrEP implementation, uptake and continued use in South Africa

To tackle the incidence of HIV in SA, the National Department of Health (NDoH) has in recent years developed guidelines and strategies for the delivery of PrEP to those at considerable risk, which includes AGYW. The NDoH first implemented PrEP as a preventative method for HIV infection in 2016, providing it to female sex workers at selected sites across the country, by 2018 access to PrEP had expanded to incorporate other key population groups at high risk such as AGYW, serodiscordant couples and MSM (17). The recently updated PrEP guidelines have also expanded access to include pregnant and breastfeeding women (18). In April 2022 approximately 416 000 people in South Africa had initiated PrEP, with much of the documented delivery being through open label clinical trials, demonstration, implementation, social and behavioral projects (19). Despite these guidelines and interventions PrEP uptake and use remains low in SA. The prevention of HIV using PrEP is often hindered by poor awareness of the intervention. The extent of PrEP awareness among young people in SA in general is considerably low, one cross-sectional study among young people aged 16 to 24 found that approximately 18% were aware of PrEP and less than 2% of them has used PrEP (20).

The definition of PrEP initiation is the uptake of PrEP by those who are offered and decide to use it while PrEP continuation is defined as the persistent use of PrEP by those who continue to be eligible for the intervention at specified sequential timepoints post uptake (21). Defining PrEP adherence is more complex and is dependent on the different clinical guidelines on methods used to measure daily pill use. There are soft measurements, such as the self-report of number of pills taken within a specific timeline, the slightly more objective measure of pharmacy or pill refill data that uses pill counts to determine the level of adherence (22). There are also more stringent and objective measurement options such as electronic adherence

monitoring that measure adherence by monitoring and recording the times pill bottles are opened daily (22). The most objective measure is the use of red blood cells, plasma or hair to measure drug levels to quantify adherence however this is the most expensive method of measurement (22).

Nonetheless, the success of PrEP in the prevention of HIV hinges on consistent use and is therefore user controlled. A meta-analysis synthesizing finding from PrEP demonstration projects, clinical studies and interventions across the world found an average adherence of approximately 65% in the first month (23). Inconsistent adherence has halted the success of PrEP implementation among AGYW, and many of the PrEP demonstration projects across southern Africa have been characterized by a high initial uptake and a rapid dropout rate. One study documented a dropout rate of 50% of AGYW enrolled in the program (24). Another study in Khayelitsha found consistently low levels of tenofovir diphosphate (TFV-DP) of in 67% of participants suggesting poor adherence (25). Studies examining PrEP persistence have also documented low rates of seroconversion during the intervention period despite the high-risk profile of the AGYW enrolled (26).

1.2 Literature Review

The literature presented in this review emphasizes the determinants of PrEP uptake and continued use among AGYW and draws on evidence from both qualitative and quantitative research, clinical trials, demonstration, and implementation projects in the African region.

1.2.1 Individual level factors related to use of PrEP

PrEP delivery projects involve the routine provision of oral PrEP to HIV negative AGYW at elevated risk of HIV infection and desire to use PrEP to prevent becoming infected with HIV. Both quantitative and qualitative research have documented the complex interplay of individual, behavioral, interpersonal, socio economic and structural level factors associated with AGYW use of PrEP.

Knowledge related factors

Research investigating the relationship between awareness and knowledge of PrEP has found an association between low PrEP awareness and low uptake. Studies have found the greatest barrier to PrEP use among AGYW is the limited knowledge of PrEP (27,28). A study among AGYW who sell sex in KwaZulu-Natal found low levels of awareness of PrEP across the group (29). Furthermore, Chimbindi *et al*., report the low level of PrEP awareness was exacerbated by the lack of availability of PrEP in the public clinics in their communities. One qualitative study conducted in Malawi among AGYW found that none of the AGYW engaging in in-depth interviews were aware of PrEP prior to the study although once they acquired this knowledge they hoped it would become available in their local clinics (30). Suggesting that PrEP acceptability and willingness to use PrEP is improved by promoting education of PrEP among AGYW.

Socio-economic related factors

Evidence shows poorer PrEP uptake and continuation among younger women than in older women in general (31). A study documenting PrEP uptake and continuation among AGYW within a clinic setting in Kenya found that PrEP uptake and continuation at month 1 was lower among AGYW aged 24 or less than in women aged 24 or older and those aged 24 and older (31). Further research has found younger AGYW have lower PrEP persistence outcomes than older AGYW (32). Poorer PrEP outcomes in AGYW can be attributed to the delay between the cognitive and emotional development that begins in adolescence up till the early 20s. Studies show neurocognitive development influences the way young people make decisions about health risks and their prevention behaviors in relation to future health benefits (33). It has also been hypothesized that PrEP persistence is more difficult for younger individuals because they also have not typically used medication for a prolonged period (34).

Marital status has been observed as a determinant of PrEP use, research findings suggest PrEP uptake is independently higher among unmarried young women those that were married (31). Researchers investigating educational attainment and PrEP use have observed that the likelihood of initiating PrEP among those who had only attained primary level education was significantly lower however those with tertiary level education were more likely to drop out from the study (25).

Behavioral and inter-personal related factors

There is conflicting evidence on the relationship between the perceived risk of HIV infection and PrEP use. One clinical trial among women initiation PrEP in Durban found lower odds of continuing with PrEP after the trial among those who thought that they would likely or eventually become infected with HIV (35). While the HPTN 082 study evaluating oral PrEP as the principle strategy to prevent HIV for AGYW in South Africa and Zimbabwe found those

who used PrEP believed they were at risk for contracting HIV had higher adherence at month 6 than those who did not believe they were at risk of contracting HIV (26). The study by Cellum *et al*., also reported high PrEP uptake (>90%) and reported a high prevalence (39%) of curable STIs among AGYW enrolled in the study suggesting a relationship between previous or current STI status and PrEP uptake.

Existing evidence suggests that AGYW who have partners living with HIV have an increased likelihood of initiating and continuing PrEP (31). Furthermore, even when AGYW are not aware of their partners HIV status studies report high PrEP initiation and increased odds of returning for follow up PrEP services (31,36). Studies have found an increased association between transactional sex or sex work and PrEP initiation (32,37,38). Additionally, Hill *et al*., report AGYW who practiced transactional sex had increased odds of being interested in PrEP (38). A study carried out in Zimbabwe among young women who sell sex (YWSS) concluded PrEP initiation was associated with having more clients in the past month as well as having a longer duration of sex work (37). Within the context of transactional sex, findings suggest AGYW regard PrEP as a means to mitigate the threat of contracting HIV (39).

Sexual relationships between AGYW and their partners are found to vary in both nature and duration. A study by Atkins et al., found that AGYW who were classified to be in shorter and riskier relationships had the highest uptake of PrEP when compared to those in stable relationships with older partners and those in shorter relationships with their peers (40). Suggesting that diverse types of relationships have an influence on the use of PrEP. Furthermore, research has shown that relationship and power dynamics such as distrust, infidelity and intimate partner violence are influential in the decision to use PrEP (41,42). Intimate partner violence (IPV) is found to be related with PrEP adherence among AGYW and that dependent on the age of the AGYW, an IPV episode can either hinder or encourage PrEP continuation (43).

Research documenting the way in which AGYW's partners and family influence the interest and ability to use PrEP has reported conflicting findings. Both qualitative and quantitative studies have reported disclosure of PrEP use as an aiding factor for PrEP uptake and continuation (35,44,45). Additionally, a study by Beesham *et al*., found the odds of continuing PrEP were 5 times higher among those who shared their use of PrEP with family, friends or partners than those who did not (35) . Supportive relationships were also reported as helpful in providing reminders to take pills (46). Suggesting that support from partners and family positively influences PrEP use and is essential to PrEP persistence.

On the contrary, other studies report experiences of stigma, unsupportive partners and the negative influence of a mother or a partner who regularly observed them taking pills have been associated with the decision to discontinue PrEP among AGYW (35,39,47). The fear of stigma has been documented as a significant impediment to initiation of PrEP. AGYW who report fear of stigma show reduced odds of PrEP uptake at onset and increased odds of missed visits or loss to follow up post initiation (36).

1.2.2 Medication related factors associated with use of PrEP

Several studies report an association between issues related to the taking of PrEP pills and PrEP use among AGYW. One of the most commonly reported factors associated with the reluctance to initiate PrEP or the discontinuation of PrEP is side effects (26,39). Furthermore, findings also suggest PrEP persistence is difficult for AGYW because they frequently forget to take their daily pill (45). On the contrary, Pintye *et al*., also found that pregnancy aided in the covert use of PrEP as pill taking is regarded as a normal part of prenatal care and that PrEP continuation was difficult postpartum (45). Studies examining PrEP uptake in pregnancy have found high uptake and high persistence of PrEP among pregnant users (36). Additionally,

where AGYW have adjusted their use of PrEP during pregnancy one their primary motivators have been concerns about the safety of PrEP for their baby (48). This highlights that pregnant AGYW are interested in using PrEP and underscores the significance of providing PrEP and addressing the drawbacks to its use especially during pregnancy when there is increased risk of HIV infection (7).

1.2.3 Health care and program related factors associated with PrEP use

In the delivery of PrEP to AGYW, researchers have found associations between programmatic factors and PrEP uptake and continuation. Studies examining PrEP uptake among AGYW in real world settings such as family planning clinics and mobile clinics have documented low initiation and high rates of PrEP drop out (31). Qualitative research exploring the influence of health care workers on an AGYW PrEP rollout program found the clinic environment was hostile towards AGYW use of PrEP and that health care workers actively stigmatized and dissuaded AGYW from using PrEP (28).

Among PrEP demonstration projects that have incorporated strategies to support PrEP adherence among AGYW have also observed higher PrEP adherence at month 3 among AGYW attending adherence clubs (26). In addition, researchers observed a positive effect of providing peer support and counselling in PrEP delivery projects documenting these were highly attended and highly appreciated by AGYW (26). Findings also suggest that using messaging platforms like WhatsApp chatgroups to offer support or as a means to send pill reminders, PrEP users reported a positive effect of this strategy throughout the study period (25,26).

In summary, the reviewed literature illustrates that PrEP uptake and continued use among AGYW is influenced by multiple determinants including socio demographic, behavioral, interpersonal, medical and program related factors. Although these findings have been obtained

using different study designs and demonstration programs involved in the delivery of PrEP to AGYW across different settings there remains a need to evaluate associated factors of PrEP uptake and continuation among AGYW within a primary health care clinic located in a high HIV burden setting.

1.3 Conceptual framework

The PrEP cascade framework is designed to monitor a continuum of care in HIV prevention service and can be used as a tool to measure PrEP uptake and continued use among AGYW (21). The framework disaggregates AGYW by PrEP use at each stage in the cascade. Its elements include (1) offer PrEP to those at elevated risk of contracting HIV, (2) identifying whether the AGYW is suitable to take PrEP, (3) linking that AGYW to PrEP services, (4) the AGYW initiation of PrEP, (5) the AGYW are retained in follow up care, (6) PrEP adherence and persistence is maintained over time (21). The PrEP cascade framework by Dunbar *et al* is shown in figure 1.1 below.

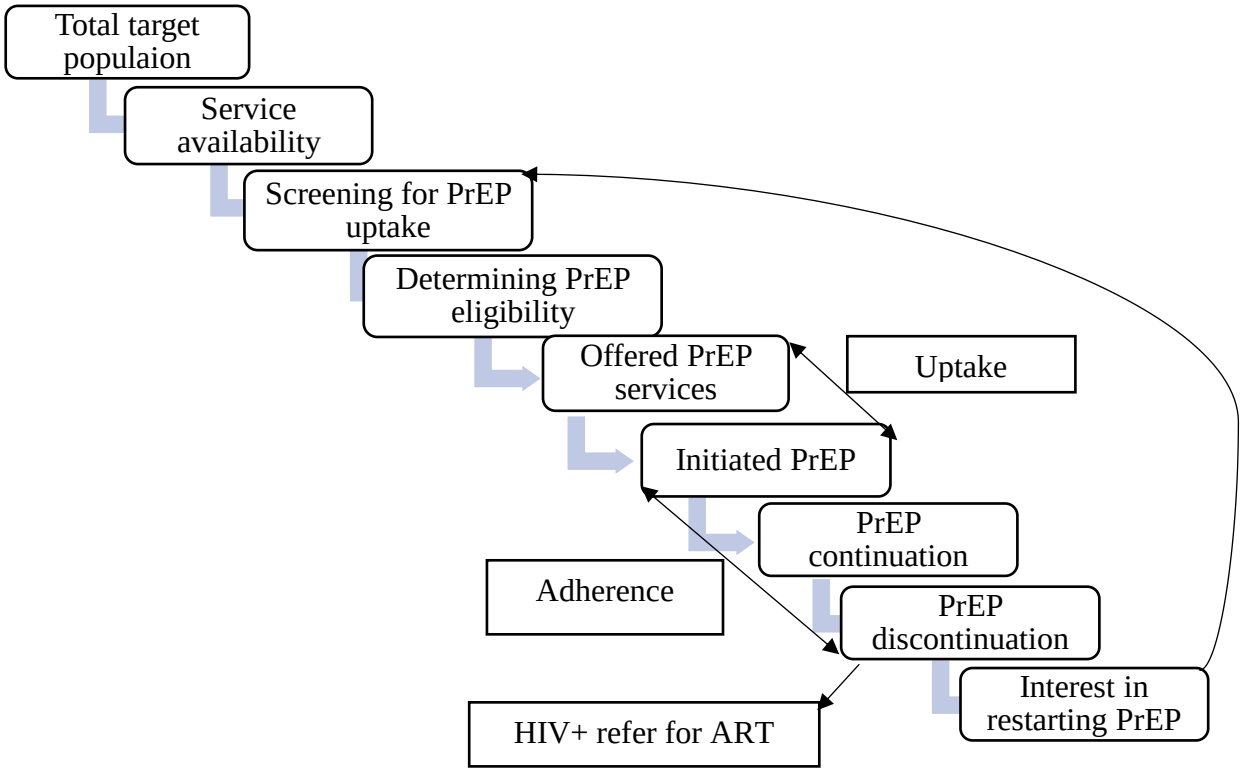

Figure 1.1: Oral pre-exposure prophylaxis (PrEP) cascade by Dunbar *et al*

This study involves secondary data analysis of programmatic data and while all the steps in the PrEP prevention cascade are valuable, this data was not captured during data collection. Thus, this study will use an adaptation of the PrEP prevention cascade and include stages in the cascade that focus on uptake and adherence. Thus, this study will make use of an adaptation of the PrEP prevention cascade in figure 1.2 below.

Figure 1.2: Adaptation of the conceptual PrEP cascade for AGYW

Furthermore, because this study will also determine the factors that support PrEP uptake and continuation, we will fit the determinants of PrEP uptake and continuation into the theoretical socio-ecological model (SEM)(49). The SEM is preventative model that recognizes health behavior is influenced by an interplay of individual, relational, and broader community factors. Within the context on HIV prevention, this theoretical model is useful in the exploration of the individual level factors and beyond that impact PrEP uptake in AGYW. We used an adaption of the SEM theoretical framework to examine the associations between PrEP uptake and continuation and consider individual factors such as (1) age, substance use, parity, contraceptive use, medical history, sexual behavior, and practices (2) relational factors such as home environment, government social assistance, partner HIV status and medical history.

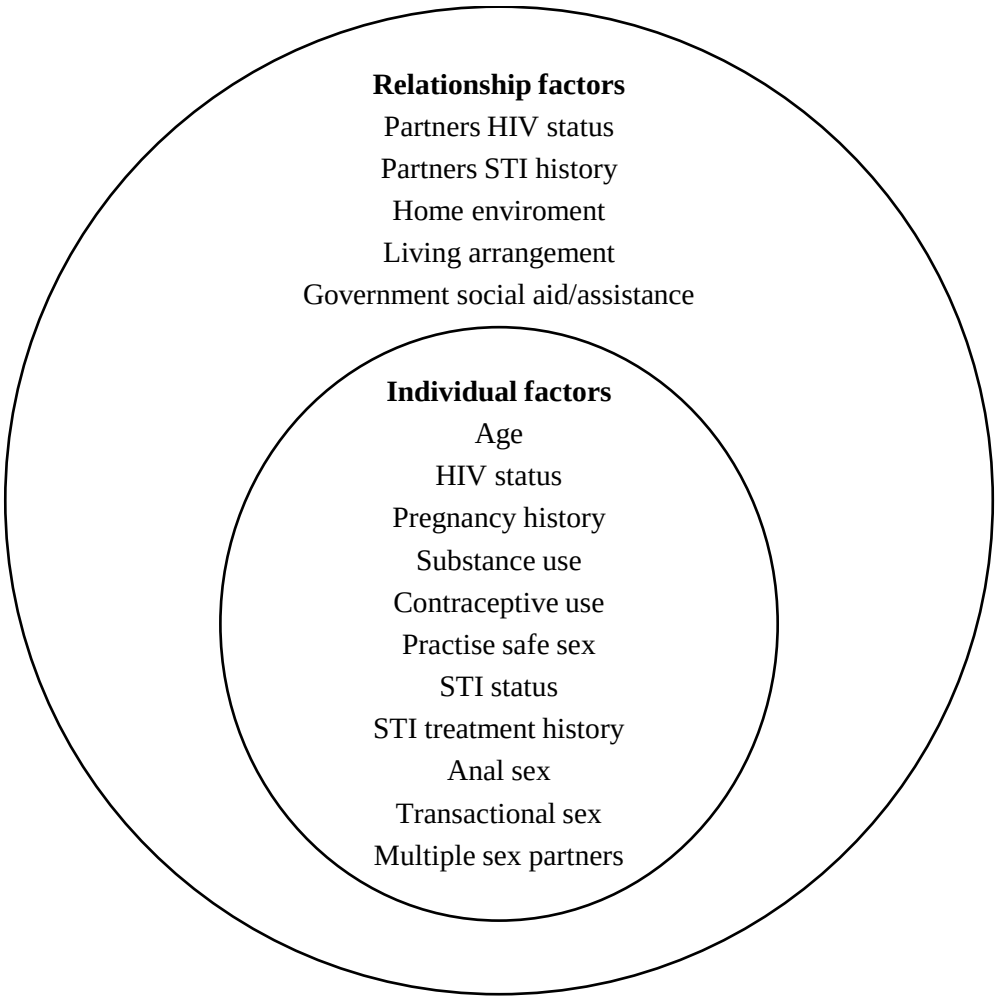

Figure 1.3: The adaptation of the socio-ecological model (SEM) theoretical framework

1.4 Problem statement

In SA, KZN has become the epicentre of the HIV epidemic and evidence shows that in 2017, 27% of people aged 15 to 49 living in in the province were infected with HIV (9,50). The province has become a hyper endemic setting for the spread of HIV among AGYW. One study carried out in rural KZN found 1 in 5 AGYW reported engaging in transactional sex or sex for money (29). It is documented that AGYW have difficulty with negotiating condom use (12), placing young women who sell sex (YWSS) at direct threat of acquiring HIV. In comparison to other HIV prevention methods, PrEP is a highly advantageous prevention method for AGYW because not only is it highly effective when adhered to it allows for autonomous and covert use (51). Despite efforts to make PrEP accessible to AGYW, PrEP awareness, uptake and use remains very low and slow among young people in general (20). An understanding of what supports the initiation and continuation of PrEP in AGYW is an area of active research that has not been extensively studied.

1.5 Justification

The unequal burden of HIV continues to plague AGYW in SA, to address the persistent high HIV incidence among AGYW and the low uptake and use of PrEP services it is especially necessary to collect evidence of factors that support PrEP uptake and continued use among AGYW within the context of a high burden setting like KZN. Findings from this research may contribute to wider implementation of PrEP delivery through primary health care clinics in SA. Empirical evidence to improve awareness and facilitate initiation and continued use of PrEP among AGYW is a top priority for the NDoH and this research will add to the body of work that will further strengthen the uptake of PrEP services among AGYW in South Africa (52).

1.6 Research question

What are the factors associated with PrEP uptake and continued use among AGYW within the HIV prevention combination program in the uMhlathuze KZN between the 1st of June 2020 and the 31st of June 2021?

1.7 Aim

The overarching aim of this study is to describe the characteristics of the AGYW initiating PrEP services and determine the associated factors of PrEP uptake and continuation among AGYW enrolled in the HIV prevention combination program in the uMhlathuze Municipality KwaZulu-Natal South Africa.

1.8 Objectives

1. Describe the characteristics of the AGYW enrolled in the HIV prevention combination program who initiated PrEP services at baseline in the uMhlathuze municipality of KwaZulu-Natal.

2. Determine the percentage of AGYW enrolled in the HIV prevention combination program who initiated PrEP services at baseline and then continued use at follow-up in in the uMhlathuze municipality of KwaZulu-Natal.

3. Identify factors associated with initiation of PrEP among AGYW enrolled in the HIV prevention combination program in the uMhlathuze municipality of KwaZulu-Natal.

4. Identify factors associated with PrEP continuation among AGYW enrolled in the HIV prevention combination program in the uMhlathuze municipality of KwaZulu-Natal.

2 CHAPTER 2: METHODOLOGY

2.1 Study design

This was a quantitative retrospective cohort study design using secondary data collected between the 1st of June 2020 and the 31st of June 2021.

2.2 Primary program

This study used programmatic data from an ongoing HIV prevention combination program for AGYW in the uMhlathuze municipality in the King Cetswayo district of KZN. The overarching objective of this program is to offer HIV testing, treatment and prevention services including PrEP to as much as 35000 in and out of school AGYW (53). The program initiated in March 2019 and is led by a public health organisation called Strategic Analytics and Management (SAM) Initiatives and its consortium partners, in collaboration with the Department of Health (DoH) in the uMhlathuze in the King Cetswayo district (53). The overarching goal of the combination program is to influence behaviour change using multiple strategies including raising awareness, counselling, and dialogue sessions with AGYW, providing sexual and reproductive health (SRH) services, and HIV treatment and prevention services. This combination program is being implemented within schools and NDoH primary health care clinics and mobile clinics in the uMhlathuze municipality. All AGYW who used these clinics were actively recruited into the program and offered PrEP and were initiated on PrEP on the basis that after being tested they were HIV negative, perceived themselves at risk for contracting HIV and had a desire to utilise PrEP for the prevention of HIV.

2.3 Setting

The provision of PrEP to AGYW is facilitated through NDoH community primary health clinics located in the uMhlathuze municipality in the King Cetswayo district of KwaZulu-Natal in the North East of Durban which is predominantly an urban area (54). Recruitment into the

program was led by PrEP mobilisers and PrEP screening was conducted by HIV testing service (HTS) counsellors at each clinic, after producing a negative HIV test all AGYW eligible for PrEP were initiated by a professional nurse.

2.4 Study population

The inclusion criteria for our sample were self-reported female at birth, HIV uninfected at baseline, adolescent girl aged 15 - 18, young women aged 19 - 24, enrolled in the PrEP program. The study population was comprised of HIV uninfected AGYW between the ages 15 - 24 that initiated the program between the 1st of June 2020 and the 31st of June 2021. We included data from participants who used PrEP in our analysis up to the point of their discontinuation, 1484 AGYW discontinued PrEP between June 2020 and June 2021.

2.5 Sampling and sample size

All 3324 records of AGYW between the ages 15 - 24 that were offered PrEP services were used in the analyses. Power was calculated using Stata V15 at an alpha level of 0.05. The power of the study was 99% to detect at least a 10% difference in the proportion between groups for the primary outcome (PrEP uptake). .

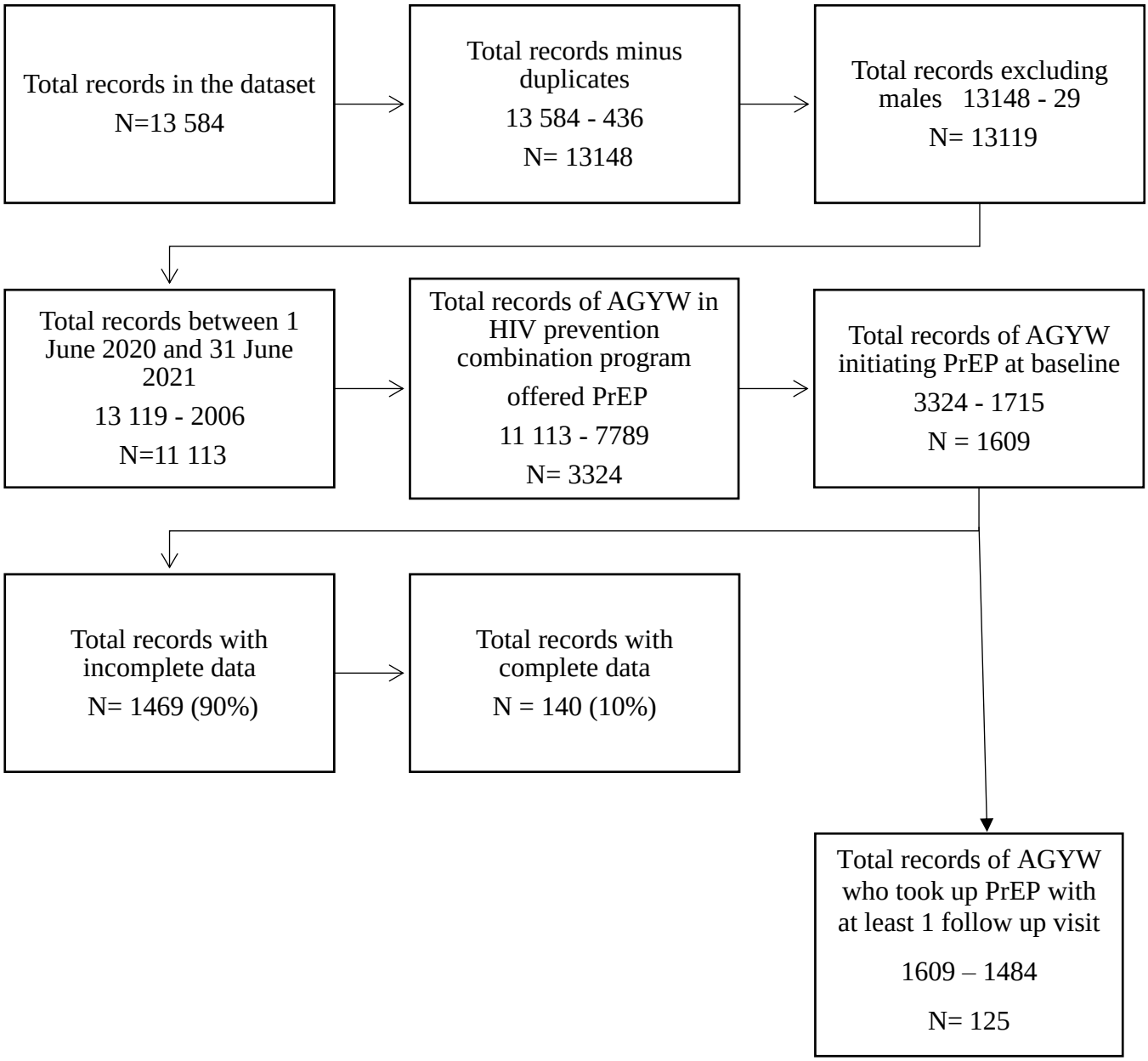

Fig 2.1: Flowchart outlining final sample size

2.6 Data collection

A biomedical form captured beneficiary data including written beneficiary informed consent obtained in person, sociodemographic details, an HIV and STI screening test report, a PrEP screening and initiation report. Information on the referral of services and an additional National Department of Health informed consent form was captured. All forms were first

checked and verified by a data validator and later captured on an electronic application called My Hope for the purposes of compiling a database for analysis and reporting.

2.7 Data management

Data management and analysis was conducted using Stata 15. Prior to analysis the dataset was cleaned and checked for missing values. Many explanatory variables had more than 70% missing data, such as educational level, employment status, home environment, living arrangement, household on social grant, used a condom at last sexual encounter, transactional sex, more than 1 sexual partner in the last 6 months, had anal sex in the previous 4 months, knows partners HIV status, parity, has living children, contraceptive use, and substance use.

Variable definitions:

Outcome variable

Our primary outcome of interest was PrEP initiation at baseline defined as the number of AGYW who were offered PrEP and initiated its use during at their first visit. Uptake of PrEP is measured using a dichotomous outcome variable, "PrEP initiation (0 = no, 1 = yes) and this was used for bivariable and multivariable analysis.

Our secondary outcome of interest was PrEP continuation at follow-up visit which in this study was defined as PrEP use at the follow up post PrEP initiation between the 1st of June 2020 and the 31st of June 2021. This study defined PrEP continuation as having at least 1 record of follow up after PrEP initiation. The continued use of PrEP was measured using a dichotomous outcome variable "PrEP continuation" (0 = no, 1= yes) and was used for bivariate analysis and multivariable analysis. Discontinuation was classified as having no record of follow up after initiating PrEP within the study timeline.

Explanatory variables

We considered a range of sociodemographic and behavioural variables to examine the factors associated baseline uptake and continued use of PrEP at follow up. Sociodemographic and biomedical data was captured at baseline using a biomedical form and program enrolment questionnaire during enrolment. Where necessary we merged categorical variables with dwindling numbers into fewer categories. Age was captured as a continuous variable and then organised into 2 categories: 15 - 18 and 19 - 24. These categories were based on the WHO definitions of adolescents and young people. The environment at home was organised in 3 categories: unsafe and unstable, overcrowded, and safe. Whom the AGYW lived with was organised in 2 categories: alone, or with both parents and a guardian. Whether or not their household received a government assistance social grant was grouped into 2 categories "household social grant" yes or no.

Biomedical information such as parity was organised into a binary variable (yes or no), whether the AGYW had any living children was categorised as a binary variable (yes or no). Contraceptive use was categorised as yes or no. Pre HIV-test-counselling provided organised as a dichotomous variable (0 = no, 1 = yes). HIV status was measured at baseline and organised as a dichotomous variable (0 = HIV negative, 1 = HIV positive). Currently on STI treatment was classified as a dichotomous variable (0 = no, 1 = yes), previous STI in the last 6 months as a dichotomous outcome (0 = no, 1 = yes).

Behavioural factors such as whether the AGYW used a condom at last sexual encounter categorised as yes or no, more than 1 sexual partner in the past 6 months categorised as yes or no. Practiced anal sex in the previous 4 months categorised as yes or no. Engaged in transactional sex was categorised as yes or no. Knowledge of partners HIV status was

categorised as yes or no. Whether their partner had an STI in the last 6 months categorised as yes or no. Substance use was categorised as yes or no.

2.8 Statistical analysis

A flow chart (figure 2.1) was utilised to outline the process of selecting our final study sample. Frequencies and percentages were used to express categorical variables. Bivariable analysis was conducted using Chi-squared and Fisher's exact test to assess associations between PrEP initiation and the explanatory categorical variables. All explanatory variables used in our bivariate analysis were used in our regression models regardless of the p value observed during bivariate analysis. Log-binomial regression was used to evaluate risk factors associated with our primary outcome (PrEP initiation) (Table 3.3) and our secondary outcome (PrEP continuation) in Table 3.4). Risk ratios (RRs) and their 95% CI were used as the measure of effect. Variables with $p<0.1$ were included in both the multivariable models for both PrEP initiation (Table 3.3) and PrEP continuation (Table 3.4) to identify factors associated with each outcome. A cut off $p<0.05$ was used in the multivariable model to identify factors related to with both the primary (PrEP initiation) and secondary outcome (PrEP continuation). Adjusted risk ratios and their 95% confidence intervals (CIs) were used as a measure of association. All statistical analyses were conducted using Stata (V.15) statistical software and RStudio.

2.9 Ethical considerations

The University of Witwatersrand Human Research Ethics Committee (Medical) approved this study, ethical approval number: M220271). Secondary data received from Strategic Analytics and Management (SAM) was anonymised and password protected.

3 CHAPTER 3: RESULTS

This chapter reports the outcome of our analysis in line with the objectives of the study. This section begins with an illustration of the sociodemographic and behavioural characteristics of the participants followed by a comparison of the characteristics between participants that declined PrEP and those that initiated PrEP services. Associations between PrEP initiation and explanatory variables are explored. Factors predicting PrEP initiation and PrEP continuation are presented using univariable and multivariable log binomial regression. Finally, an identification and report of the variables associated with both PrEP initiation and PrEP continuation after the adjusted multivariable analysis are shown.

3.1 Description of the study population

A total of 3324 records of AGYW who beneficiaries in the HIV prevention program between the 1st of June 2020 and the 31st of June 2021 were used in our analysis. Figure 3 outlines the process of selecting our study participants. Table 3.1 summarises the characteristics of the study participants.

Table 3.1: Characteristics of AGYW enrolled in the HIV prevention program in the uMhlathuze, KwaZulu-Natal (N=3324)

Variable		**n (%)** **N=3,324**
Age categories	15-18	1,207 (36.3%)
	19-24	2,117 (63.7%)
Pre HIV-test counselling provided	No	921 (27.7%)
	Yes	2402 (72.3%)
Baseline HIV status	HIV negative	3,291 (99.1%)
	HIV positive	3 (0.09%)
PrEP initiation	No	1715 (55.6%)
	Yes	1609 (48.4%)
PrEP continuation	No	1484/1609 (92%)
	Yes	125/1609 (8%)
Environment at home	Unsafe and unstable	73 (2.1%)
	Overcrowded	19 (0.6%)
	Safe	1,426 (42.9%)
Household receives a social grant	No	1,407 (42.3%)
	Yes	126 (3.8%)
AGYW living arrangement	Alone	700 (46%)
	Parent / Guardian	823 (54%)
Used condom at last sex	No	678 (20.1%)
	Yes	857 (25.8%)
Currently on STI treatment	No	3,117 (93.8%)
	Yes	207 (6.2%)
Had STI in last 6 months	No	3,186 (95.8%)
	Yes	138 (4.2%)
Transactional sex in last 6months	No	421 (12.7%)
	Yes	590 (17.7%)
> 1 sex partner in last 6 months	No	881 (26.5%)
	Yes	559 (16.8%)
Had anal sex in the last 6 months	No	1,113 (33.5%)
	Yes	208 (6.3%)
Knows partners HIV status	No	835 (25.1%)
	Yes	696 (20.9%)
Partner had an STI in last 6mnths	No	1,420 (42.7%)
	Yes	11 (0.3%)
Ever been pregnant	No	977 (29.4%)
	Yes	569 (17.1%)
Has children that are alive	No	989 (29.8%)

	Yes	551 (16.6%)
Currently using contraception	No	375 (11.3%)
	Yes	248 (7.5%)
Uses substances	No	1,049 (31.6%)
	Yes	433 (13%)

Note: Unless otherwise indicated, totals that amount to less than 3324 indicate missing data;
* % calculated as n/N.

A total of 3324 AGYW were offered PrEP services, of these 52% (N=1715) declined PrEP and 48% (N=1609) initiated PrEP services. Of those that initiated PrEP services, only 8% (N=125) had at least 1 record of follow-up post initiation and 92% (1484) had no record of PrEP continuation. At baseline, three quarters (72%) of the AGYW received counselling prior to taking an HIV test. Based on the rapid HIV test results majority (99%) of participants were HIV negative, and 3 tested positive for HIV at enrolment and could not initiate PrEP services. Of those that were HIV negative at enrolment(N=3291), approximately 49% (N=1609) initiated PrEP services and 51% (N=1715) did not. More than a third (43%) of the AGYW reported living in a safe home environment and approximately 42% (N=1407) of the AGYW did not reside in a home that received a government assisted social grant. Approximately quarter (N=857) of the participants used a condom at their last sexual encounter, 94% were not on any STI treatment at baseline and 4% (N=138) reported having an STI in the 6 months prior to the study period. Eighteen percent of the participants practiced transactional sex, 26% had more than 1 sex partner in the last 6 months. One quarter (N=835) of the AGYW were ignorant of their partners HIV status and 42% reported their partner did not have an STI in the last 6 months. Over 25% of participants had been pregnant (N=977) and had living children (N= 989) and 13% of the study participants reported using substances

3.2 Bivariable analysis

Bivariable analysis was performed to compare differences between those who declined PrEP services and those that initiated PrEP for each explanatory variable under investigation. The results are presented in Table 3.2 below.

Table 3.2: Comparison of AGYW enrolled in the HIV prevention program that were offered and initiated PrEP services in the uMhlathuze, KwaZulu-Natal (N=3324)

Variable	Declined PrEP	Initiated PrEP	Test statistic	P-value
	N=1715	N=1609		
Age category				
15-18	734 (42.8%)	473 (29.4%)	$\chi2$ = 64.2	<0.001*
19-24	981 (57.2%)	1136 (70.6%)		
Pre-HIV test counselling provided				
No	0(0%)	921(100%)		<0.001*†
Yes	1715 (71%)	687(29%)		
Baseline HIV status				
HIV Negative	1,682 (51.1%)	1,609 (48.8%)		0.250†
HIV Positive	3 (0.2%)	0 (0.0%)		
Environment at home				
Unsafe and unstable	59 (5.4%)	14 (3.3%)		0.102†
Overcrowded	16 (1.5%)	3 (0.7%)		
Safe	1,013 (93.1%)	413 (96.0%)		
Household receives social grant				
No	1,005 (91.7%)	402 (92.0%)	$\chi2$ = 0.04	0.85
Yes	91 (8.3%)	35 (8.0%)		
AGYW living arrangement				
Alone	538 (76.9)	162 (23.1)	$\chi2$ = 17.4	<0.001*
Parents/ Guardian	553 (67.1)	270 (32.8)		
Used condom at last sex				
No	545 (49.9%)	133 (30.0%)	$\chi2$ = 51.3	<0.001*
Yes	547 (50.1%)	310 (70.0%)		
Currently on STI treatment				
No	1,708 (99.6%)	1,409 (87.6%)	$\chi2$ = 205.6	<0.001*
Yes	7 (0.4%)	200 (12.4%)		
Had STI in the last 6 months				
No	1,681 (98.0%)	1,505 (93.5%)	$\chi2$ = 41.9	<0.001*
Yes	34 (2.0%)	104 (6.5%)		
Transactional sex in last 6 months				
No	302(43.6%)	119(37.3%)	$\chi2$ = 3.5	0.063

Yes	390 (56.4%)	200 (62.7%)		
> 1 sex partner in last 6 months				
No	646 (62.1%)	235 (58.8%)	$\chi2 = 1.5$	0.227
Yes	394 (37.9%)	165 (41.3%)		
Had anal sex in last 6 months				
No	834 (86.7%)	279 (77.7%)	$\chi2 = 15.1$	<0.001*
Yes	128 (13.3%)	80 (22.3%)		
Knows partners HIV status				
No	615 (56.4%)	220 (49.9%)	$\chi2 = 5.6$	0.018*
Yes	475 (43.6%)	221 (50.1%)		
Partner has STI in last 6 months				
No	1,034 (99.3%)	386 (99.0%)	$\chi2 = 0.5$	0.493
Yes	7 (0.7%)	4 (1.0%)		
Ever been pregnant				
No	746 (67.7%)	231 (52.0%)	$\chi2 = 33.8$	<0.001*
Yes	356 (32.3%)	213 (48.0%)		
Has living children				
No	756 (68.8%)	233 (52.8%)	$\chi2 = 34.9$	<0.001*
Yes	343 (31.2%)	208 (47.2%)		
On contraceptives				
No	252 (61.2%)	123 (58.3%)	$\chi2 = 0.5$	0.460
Yes	160 (38.8%)	88 (41.7%)		
Uses substances				
No	797 (72.8%)	252 (65.1%)	$\chi2 = 8.1$	0.004*
Yes	298 (27.2%)	135 (34.9%)		

Variables with $p \leq 0.05$ were statistically significant; *†* p-values with no corresponding test statistic were obtained using Fisher's exact test.

The following are variables found to be significantly associated with PrEP initiation; Age category (χ 2= 64.2, p<0.001), Pre HIV-test counselling provided (p<0.001), condoms provided (p<0.001), AGYW living arrangement (χ 2= 65.5, p<0.001), used condom at last sex (χ 2 = 51.3, p<0.001), currently on STI treatment (χ 2= 205.6, p<0.001), had STI in last 6 months (χ 2=41.9, p<0.001), had anal sex in last 6 months (χ 2= 15.1, p<0.001), knows partners HIV status (χ 2= 5.6, p = 0.018), ever been pregnant (χ 2= 33.8, p <0.001), has living children (χ 2= 34.9, p<0.001), and uses substances (χ 2= 8.1, p=0.004) Table 3.2.

3.3 Factors associated with PrEP initiation among AGYW enrolled in the HIV prevention program services in uMhlathuze, KwaZulu-Natal

Univariable log binomial regression

Table 3.3 below outlines the results of the both the unadjusted and adjusted analysis.

Table 3.3: Factors associated with PrEP initiation among AGYW enrolled in the HIV prevention program in uMhlathuze, KwaZulu-Natal (N=1609)

Variable	Initiated PrEP N=1609	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Age category			
15-18	473 (29.4%)	1	1
19-24	1,136 (70.6%)	1.4 (1.3 – 1.5) ****	0.9 (0.7 – 1.1)
Environment at home			
Unsafe and unstable	14 (3.3%)	1	1
Overcrowded	3 (0.7%)	0.8 (0.3 -2 .6)	0.6(0.2 - 2)
Safe	413 (96.0%)	1.5 (0.9 - 2.4) *	1.3(1 – 1.6) **
AGYW living arrangement			
Alone	162 (23.1)	1	1
Parents/Guardian	270 (32.8)	1.4 (1.2-1.7) ****	1(0.8 – 1.2)
Household received social grant			
No	402 (92.0%)	1	
Yes	35 (8.0%)	0.97 (0.7 -1.3)	
Used a condom at last sex			
No	133 (30.0%)	1	1
Yes	310 (70.0%)	1.9 (1.6 -2.2) ****	1.8(1.2-2.8) ***
Currently on STI treatment			
No	1,409 (87.6%)	1	1
Yes	200 (12.4%)	2.1 (2 – 2.2) ****	1.7(1.2-2.3) ****
Had STI in last 6 months			
No	1,505 (93.5%)	1	1
Yes	104 (6.5%)	1.6 (1.4 – 1.8) ****	2.1(1.5-2.8) ****
Transactional sex in last 6 months			
No	119 (37.3%)	1	1
Yes	200 (62.7%)	1.2 (1 -1.4) *	1(0.8 – 1.2)
> 1 sex partner in last 6 months			
No	235 (58.8%)	1	
Yes	165 (41.3%)	1.1 (0.9 – 1.3)	
Had anal sex in last 6 months			

No	279 (77.7%)	1	1
Yes	80 (22.3%)	1.5 (1.2 – 1.9) ****	0.9(0.8 – 1.2)
Knows partners HIV status			
No	220 (49.9%)	1	1
Yes	221 (50.1%)	1.2 (1 – 1.4) **	1(0.7 – 1.2)
Partner had STI in last 6 months			
No	386 (99.0%)	1	
Yes	4 (1.0%)	1.3 (0.6 – 2.9)	
Ever been pregnant			
No	231 (52.0%)	1	1
Yes	213 (48.0%)	1.6 (1.4 – 1.9) ****	1.4(0.6 – 3.2)
Has living children			
No	233 (52.8%)	1	1
Yes	208 (47.2%)	1.6 (1.4 -1.9) ****	0.9(0.4 - 2)
On contraception			
No	123 (58.3%)	1	
Yes	88 (41.7%)	1.1 (0.9 – 1.4)	
Uses substances			
No	252 (65.1%)	1	1
Yes	135 (34.9%)	1.3 (1.1 – 1.5) ***	1.2(0.9 - 1.5)

For univariable analysis variables with p≤0.1 were regarded as statistically significant. In the multivariable analysis Variables with p≤0.05 were regarded statistically significant. Variables with p≤0.001 ****, variables with p≤0.01 ***, variable with p≤0.05 **, variables with p≤0.1*

The unadjusted analysis identified the following variables as statistically significant risk factors associated with PrEP uptake among AGYW: age category, environment at home, AGYW living arrangement, used condom at last sex, currently on STI treatment, Had an STI in the last 6 months, had transactional sex in the last 6 months, had anal sex in the 6 months prior to enrolment, knows partners HIV status, ever been pregnant, has living children and uses substances.

The unadjusted univariable analysis identified environment at home as a significant risk factor associated with PrEP initiation. Participant that reported living in a safe home environment had a 50% (RR: 1.5, CI:0.9 - 2.4, p=0.091) increased likelihood of initiating PrEP services than those who lived in either an overcrowded or unsafe and unstable home environment. Age category was a significant predictor for PrEP initiation and those aged 19 – 24 had 40% increased likelihood (RR: 1.4, CI:1.3 – 1.5, p<0.001) of initiating PrEP services compared to those aged 15 - 18.

Relative to AGYW who lived alone, AGYW that lived with their parent(s), or a guardian were 1.4 times as likely (RR: 1.4, CI:1.2 – 1.7, p<0.001) to start PrEP services. Participants who used a condom at last sex had a 90% increased likelihood (RR: 1.9, CI:1.6 -2.2, p<0.001) of initiating PrEP relative to those who did not use a condom at their last sex. Those who were currently taking treatment for an STI had 2.1 times as likely (RR:2.1, CI:2 – 2.2, p<0.001) to enrol in PrEP services compared to those that were not on STI treatment. Furthermore, those who had an STI in the 6 months prior had a 60% increased risk (RR:1.6, CI:1.4 – 1.8, p<0.001) of initiating PrEP services when compared to those that did not report a STI six months prior to PrEP initiation.

In contrast, those who did not practice transactional sex, those who had transactional sex in the 6 months prior to PrEP uptake had a 20% increased likelihood (RR:1.2, CI:1 -1.4, p=0.065) of

enrolling in PrEP services. Participants who practiced in anal sex in the 6 months prior to the study showed a 50% increased risk (RR:1.5, CI:1.2 – 1.9, p<0.001) of initiating PrEP compared to those who had not had anal sex within the same period. The likelihood of starting PrEP increased by 20% (RR:1.2, CI:1 – 1.4, p=0.018) among participant who were aware of their partners HIV status contrary to those that were not aware. The likelihood of enrolling in PrEP services increased by 60% for both participants who had been pregnant (RR:1.6, CI:1.4 -1.9, p<0.001) and had living children (RR:1.6, CI:1.4 -1.9, p<0.001) compared to those that had never been pregnant and did not have any living children. Relative to those who did not use substances, those that did use substances had 1.3 times as likely (RR:1.3, CI:1.1 – 1.5, p=0.004) of taking up PrEP services.

Multivariable model

Variables that remained statistically significant predictors of PrEP initiation were had STI in the last 6 months, currently on STI treatment and used condom when they last had sexual intercourse. Participants who reported an STI in the previous 6 months were twice as likely (RR:2, CI: (1.5-2.8, p<0.001) to have initiated PrEP than those that did not report having an STI in the prior 6 months. Relative to those who were not on any STI treatment, participants that were currently taking STI treatment had an approximately 60% increased likelihood (RR:1.6, CI: 1.2-2.3, p=0.004) of initiating PrEP services. The likelihood of enrolling in PrEP services increased by 80% (RR:1.8, CI: 1.2-2.8, p=0.007) among those who used a condom at their last sexual encounter relative to those participants that did not.

3.4 Factors associated with the continuation of PrEP services among AGYW enrolled in PrEP services with at least 1 follow up visit in uMhlathuze, KwaZulu-Natal

Univariable log binomial regression

Table 3.4 below elucidates the factors associated with PrEP continuation and the magnitude of these relationships. The results of both the unadjusted and adjusted analysis are presented below.

Table 3.4: Factors associated with PrEP continuation among AGYW enrolled in PrEP services with at least 1 follow up visit in uMhlathuze, KwaZulu-Natal (N=125)

Variable	Continued PrEP	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
	N=125		
Age category			
15-18	47 (37.6%)	1	
19-24	78 (62.4%)	0.7 (0.5 -1.0) **	0.9(0.5 – 1.5)
Environment at home			
Unsafe and unstable	1 (1.9%)	1	
Overcrowded	1 (1.9%)	4.7 (0.4 – 55.5)	
Safe	50 (96.2%)	1.7 (0.3 -11.4)	
Household receives social grant			
No	50 (90.9%)	1	
Yes	5 (9.1%)	1.15 (0.5-2.7)	
AGYW living arrangement			
Alone	27 (16.7%)	1	
Parents/ Guardian	27 (10%)	0.6 (0.3-0.9)	
Used condom at last sex			
No	11 (20.0%)	1	
Yes	44 (80.0%)	1.7 (0.9-3.2) *	1.7(0.9 – 3.3)
Currently on STI treatment			
No	115 (92.0%)	1	
Yes	10 (8.0%)	0.61 (0.3-1.1)	
Had STI in the last 6 months			
No	113 (90.4%)	1	
Yes	12 (9.6%)	1.5 (0.9-2.7)	
Transactional sex in last 6 months			
No	18 (40.9%)	1	
Yes	26 (59.1%)	0.9(0.5-1.5)	
> 1 sex partner in last 6 months			
No	28 (54.9%)	1	
Yes	23 (45.1%)	1.2 (0.7-2.0)	
Had anal sex in the last 6 months			
No	37 (75.5%)	1	

Yes	12 (24.5%)	1.1 (0.6-2.1)
Knows partners HIV status		
No	22 (40.0%)	1
Yes	33 (60.0%)	1.5 (0.9-2.5)
Partner has STI in last 6 months		
No	50 (98.0%)	1
Yes	1 (2.0%)	1.9 (0.3-10.7)
Ever been pregnant		
No	23 (41.8%)	1
Yes	32 (58.2%)	1.5 (0.9-2.5)
Has living children		
No	24 (44.4%)	1
Yes	30 (55.6%)	1.4 (0.8-2.3)
On contraception		
No	17 (68.0%)	1
Yes	8 (32.0%)	0.7 (0.3-1.5)
Uses substances		
No	26 (55.3%)	1
Yes	21 (44.7%)	1.5 (0.9-2.6)

For univariable analysis variables with p≤0.1 were regarded as statistically significant. In the multivariable analysis Variables with p≤0.05 were regarded statistically significant. Variables with p≤0.001 ****, variables with p≤0.01 ***, variable with p≤0.05 **, variables with p≤0.1*

Results from the unadjusted univariable analysis found the following variables to be statistically significant risk factors for PrEP continuation; age category and used condom at last sex. Participants who were in the age category 19-24 had approximately 30% increased likelihood (RR:0.7, CI:0.5-1.0, p=0.036) of continuing PrEP services than participants in the 15 – 18 age categories. Those that disclosed condom use at their last sexual encounter had 70% increased likelihood (RR: 1.7, CI:0.9-3.2, p=0.092) of continuing PrEP use. None of the statistically significant variables in the univariable analysis remained statistically significant predictors of PrEP continuation in the multivariable model.

4 CHAPTER 4: DISCUSSION

This study aimed to determine the proportion of AGYW initiating PrEP services and the associated factors of young women's enrolment and continued use of PrEP in the HIV prevention combination program. This chapter discusses the findings obtained in relation to evidence from prior research. This chapter opens with a discussion of the results with respect to the study objectives. It closes with a reflection of the study limitations and a summary of recommendations for HIV prevention programs offering PrEP to AGYW and further research.

4.1 Oral PrEP initiation and continuation

At baseline, the HIV prevalence among participants enrolled in the HIV prevention program within the study period was less than 10%, this is similar to prior evidence in which the HIV prevalence was approximately 11% among AGYW that participated in HIV prevention programmes (55). We observed moderate initiation of PrEP and less than half (48%) of the HIV negative AGYW enrolled in the HIV prevention program that were offered PrEP services initiated its use. This finding is in line with data from other evidence with PrEP uptake among AGYW ranging between above 30 to 95%(26,56,57) . Nonetheless the aim of the above-mentioned studies was to measure PrEP uptake and adherence whilst in our study PrEP services formed part of a broader HIV prevention package for a program targeting AGYW.

Only 8% of the AGYW who initiated PrEP services had at least one record or follow up / continuation and this study reported a substantial proportion of discontinuation (92%). This is much higher than that reported by other studies among AGYW in similar settings, with PrEP discontinuation ranging between 48% and 50%(58). While existing evidence suggests that young women using PrEP may have more difficulty taking their daily PrEP pill than older PrEP users. A plausible reason for this is oral PrEP is also a preventative drug that is needed and used during periods of potential exposure to HIV such as when one has multiple sexual partners, or partner HIV status is unknown, and this may not be the case throughout one's

lifespan. Qualitative evidence suggests that AGYW practice intentional pausing of PrEP use with shifts in relationships status either when they become single or transition to more committed long-term relationships (59). Furthermore, Velloza and colleagues found high PrEP adherence was associated with HIV risk suggesting that AGYW utilise PrEP during periods of risk (60).

The scourge of the COVID-19 pandemic at the time of this study may provide a possible explanation for the high discontinuation of PrEP use. The lockdown restrictions implemented to curb the transmission of COVID-19 in March 2020 restricted movement and thus impeded access to services at health facilities or community-based programmes. One study in the Eastern Cape found a significant decline in returning visits among AGYW enrolled in a community PrEP programme during the pandemic (61). In other qualitative studies, respondents expressed that they stopped using PrEP because they had transport issues and weren't able to travel when they ran out of PrEP pills during the lockdown (62,63). Thus, it is possible that the high PrEP drop out observed in this study can be attributed to the COVID-19 lockdown restrictions in place at the time.

4.2 Factors associated with uptake of PrEP

The effect of age on PrEP initiation

Majority (71%) of the PrEP initiates were aged 20 - 24. Participants aged 20 to 24 had an increased likelihood of initiating PrEP services compared to those aged 15 to 19. Furthermore, individuals who were aged 20 - 24 had approximately 30% increased likelihood of continuing PrEP services compared to those aged 15 – 19.

This is echoed in a study by Patel et al., that found the proportion of PrEP uptake among AGYW aged 20 - 24 was significantly higher than those in the younger age category (56). A possible reason for this is that adolescent girls may experience greater PrEP related stigma than

young women. Kayesu *et al*., found that AGYW younger than 19 were less interested in using PrEP because of their age, which presented as a barrier to use because of fear of being judged for being sexually active at their age (64). It is equally important to highlight that this HIV prevention combination program was implemented in a primary health clinic and AGYW have reported experiencing stigma when accessing PrEP in this setting. A mixed method study conducted in SA reported more than 25% of AGYW accessing services at the clinic, and 75% providers in the study had concerns about providing PrEP to AGYW citing it would increase promiscuity, STI and pregnancy rates(65).

The effect of parity on PrEP initiation

Participants who reported having been pregnant and those who had living children had an increased likelihood of initiating PrEP compared to those who had never been pregnant and those who did not have any living children. This has not been documented before and thus cannot be critiqued with previous evidence. However, studies have shown high PrEP initiation among pregnant AGYW and women in general and uptake was associated with early gestational age(66). The threat of acquiring HIV during pregnancy is elevated and evidence suggests it is safe to use PrEP during pregnancy and effective at preventing HIV especially among serodiscordant couples (67). Therefore, although the participants in our study were not pregnant at the time of the study it is possible that they were aware of the protective benefit of PrEP for themselves and consequently their offspring.

The effect of home environment on PrEP initiation

In our unadjusted analysis, PrEP uptake was positively associated with living with a parent/s or guardian and living in a safe home environment relative to those that lived alone, and in an unsafe or overcrowded home. A possible explanation for this is young people living with a parent or guardian may have a supportive home environment and receive encouragement to

use PrEP. This is in line with other research which has shown supportive relationships positively influence the use of PrEP among young women and that environmental factors influence PrEP uptake(68).

The effect of substance uses on initiation of PrEP

We found an increased likelihood of initiating PrEP among AGYW that used substances relative to those that did not use substances. It is possible that these individuals are aware of their increased vulnerability to HIV because of their risky behaviour and altered ability to practice safe sex and a consequence of their substance use. Previous research has shown the use of drugs and alcohol increase the risk of acquiring HIV among adolescents because it is associated with early and unsafe sex, and the impaired ability to negotiate condom use (69,70). Contrary to our findings, a study by Bonner *et al*., investigating opportunities for PrEP among AGYW drug users did not find a relationship between PrEP and drug use. However, the study documented increased willingness to use PrEP, as 70% of the participants were keen to initiate PrEP if available.

The effect of condom use on PrEP initiation and continuation

Participants that disclosed condom use at their last sexual encounter had a 90% increased likelihood of initiating PrEP services relative to those who did not. This relationship remained significant in the multivariable analysis. Furthermore, we observed a positive association between PrEP continuation and condom use by AGYW at their last sexual encounter. Although this relationship did not remain significant in the multivariable analysis. Other research has demonstrated consistent condom use among PrEP users(71,72). It is pertinent to underscore that the use of condoms extends beyond HIV prevention and AGYW are aware of their ability to prevent unintended pregnancy, thus it is unlikely that PrEP use will impact the use of condoms as a contraceptive. This is echoed in a qualitative study by Sentoogo-Ssemata *et al*.,

in which AGYW expressed PrEP could not prevent unintended pregnancy and STIs thus the need to supplement condom use with PrEP(73).

The effect of transactional sex on PrEP initiation

Approximately 12% of the AGYW in this study practiced transactional sex in the previous 6 months, similar to prior PrEP research among AGYW in KwaZulu-Natal(29). We observed a positive association with PrEP uptake among individuals that practiced transactional sex compared to those that did not practice transactional sex. Our findings align with evidence that suggest PrEP use is related to the perception of risk among AGYW who engage in transactional sex. A study among YWSS in Zimbabwe also observed a positive association between PrEP uptake and transactional sex throughout the study and PrEP use was significantly higher among those reporting more than 10 clients a month(74) .

The effect of anal sex on PrEP initiation

In our unadjusted analysis there was overwhelming evidence suggesting an increased likelihood of PrEP uptake among participants that had anal sex in the last 4 months. This has not been documented before among AGYW engaging in heterosexual anal sex and therefore is not comparable to existing research. However, research shows an association between heterosexual anal sex and inconsistent condom use and pregnancy prevention(75,76). Qualitative research also highlights that even when young women desire to use condoms for HIV and pregnancy prevention their ability to negotiate condom use is limited due to limited decision-making power and the threat of intimate partner violence(12). Therefore, it is possible that within the context of heterosexual anal sex the impaired ability to negotiate condom use especially where they are not used as a contraceptive functioned as a motivator for initiating PrEP among AGYW that this study.

The effect of knowledge of partner HIV status on PrEP initiation

We observed a 20% increased likelihood of initiating PrEP pills among those who had knowledge of their partners HIV status compared to those ignorant of their partners HIV status. This finding is inconsistent with other research among AGYW in which increased PrEP enrolment and higher odds of PrEP continuation was associated with a lack of knowledge of their partners HIV status(36). Conversely, other research has found increased PrEP initiation and continuation was related to having a partner living with HIV(31). Although our study participants did not disclose their partners HIV status, a possible explanation for our finding is that they may have a serodiscordant partner and wanted to prevent themselves from contracting HIV.

The effect of STI status and treatment on PrEP initiation

Of those individuals that initiated PrEP, 12% were currently taking treatment for an STI. This finding in not in line with other studies which have documented substantially higher proportions of AGYW infected with treatable STIs at baseline(77). We observed that current or prior STI infection was positively associated with PrEP uptake. Participants that were on STI treatment were twice as likely to begin using PrEP relative to those who were not on STI treatment. Furthermore, the likelihood of enrolling in PrEP services was higher among those who were infected with an STI in the previous 6 months than those who did not report an STI in that period. This may indicate that AGYW who currently or previously had an STI may have had a higher HIV risk perception, were aware of their higher risk profile and had the desire to prevent HIV. Qualitative research has shown a key facilitator to uptake of PrEP among AGYW who believed themselves at increased risk of contracting HIV and had the desire to protect themselves(64,78). These associations remained significant in our multivariable analysis.

Therefore, this further underscore that PrEP is an intervention for groups at elevated risk for HIV who similarly are at considerable risk for STIs.

4.3 Limitations

This study highlighted key factors associated with PrEP initiation and continuation to better understand PrEP use in AGYW using real world routinely collected data. The unique opportunity to use data that is not part of a controlled environment such as clinical trials or cohorts provides insight to understand what supports PrEP initiation and continued use among AGYW in a clinical setting.

Despite this there are a few key limitations of this study. We used secondary data, and this data were collected to achieve different objectives than our study aimed to achieve, which did not allow for analysis of variables that were not collected as part of the programme's objectives. Other studies have examined seroconversion relative to PrEP use and PrEP adherence support strategies which have been found to support continued use of PrEP in AGYW(26,44). However, this data was not collected thus we were unable to examine the impact of these in this study. In future, information on routine data on seroconversion and the strategies that support PrEP uptake and persistence should be prioritised.

A large amount of missing data was observed across several explanatory variables and multiple variables had to be recoded. Thus, it is possible that associations between some explanatory variables and PrEP initiation and continuation remained undetected. The use of this real world routinely collected data also presented challenges in this study due to possible poor data entry or lack of quality control mechanisms during the data entry process. The setting for this study may have also acted as a limitation. This PrEP program was implemented in a clinical environment and the timing of the study occurred during the COVID-19 pandemic and subsequent lockdowns implemented in SA. It is possible that PrEP service disruptions and

restricted access to clinics may have occurred, and this may have altered PrEP continuation among these participants.

We used a self-reported soft measure for our secondary outcome (PrEP continuation) using PrEP refill return dates, furthermore PrEP return dates were not consistently spaced out and data on the amount of PrEP refills given was not captured. This may have introduced reporting bias as it is possible that participants may have reported inaccurate information at their return visit. Other studies have mitigated this by using more objective measures such as pill counts and blood samples to monitor continued use of PrEP pills and drug levels(26).

4.4 Conclusion

This study observed a moderate level of PrEP initiation among AGYW aligned to other studies in the African continent. The continued use of PrEP in this study was poorer than that observed in prior research and more than 90% of PrEP initiates had no record of follow up use. It is possible that lockdown restrictions implemented to curb the transmission of COVID-19 at the time of the study may have resulted in PrEP service disruptions and impeded access to services. However, this has revealed a critical need for more innovative PrEP delivery models for programs implemented in real world settings. We observed statistically significant associations between the PrEP uptake and the use of condoms at last sexual encounter, current STI diagnosis and STI diagnosis in the prior 6 months. We learned the use of condom at last sex was common among PrEP initiates. We found many AGYW currently taking STI treatment and those who had an STI in the last 6 months elected to use PrEP pills. The findings from this study calls for HIV combination prevention programs offering PrEP to provide more integrated STI prevention and treatment and innovative service delivery models to support PrEP adherence for AGYW.

4.5 Recommendations

This study underscores the principle that PrEP is an intervention for populations at elevated risk of contracting STIs and at equally substantial risk of acquiring HIV. Therefore, PrEP programs have the potential to also focus on STI prevention and treatment and should actively integrate STI services with appropriate testing approaches and targeted vaccination for high-risk groups such as AGYW. This may also be useful in conducting surveillance of STI infection and resistance in this population.

Our findings also indicate that the pandemic may have hampered the success of the PrEP intervention in this program. Therefore, there is a need for more innovative service delivery models that will support and sustain PrEP use when barriers to accessing PrEP at facilities occur. Programs should consider telehealth approaches including mobile technologies, direct to client delivery of PrEP pills and the option to collect medication from community centres. This approach will de-medicalize PrEP delivery and provide AGYW with more options that support that continued use of PrEP medication in the context of lockdowns and travel restrictions. Other PrEP interventions across the world adopted a telehealth delivery strategy to ensure continued access during the COVID-19(79,80). Furthermore, it is necessary that all HIV combination programs offering PrEP also offer adherence support strategies such as counselling, support groups, incentives, and mobile message reminders.

4.6 Suggestions for further research

This study underscored the need to better understand PrEP uptake and continued use among AGYW enrolled in a broader HIV prevention program delivered in community clinics to provide evidence of factors that support PrEP uptake and persistence within this setting.

While our study only utilised quantitative methodology, future study designs should include mixed methodology. Qualitative techniques such as in-depth interviews and focus group discussions will explore the nuanced individual enablers and barriers that influence PrEP initiation and continuation. The qualitative component will reinforce findings from the quantitative analysis and give reasons for some of the observations.

Furthermore, within the context of HIV combination prevention programs that offer other interventions in tandem with PrEP it is imperative that future research examines those who did not enrol in the PrEP intervention and elected to use other prevention technologies. Finally, where PrEP interventions are implemented in real clinical settings it may be important to examine the structural and human resources available in the setting to understand and compare PrEP outcomes.

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6 APPENDICES

6.1 Appendix 1: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:	Ms JJS Methazia School of Public Health Division of Epidemiology and Biostatistics Medical School University E-mail: 1149647@students.wits.ac.za
CC:	Supervisor: Professor P Nyasulu <pnyasulu@sun.ac.za> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2022/05/17
REF:	R14/49
PROTOCOL NO:	**M220271** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*Factors associated with uptake of pre-exposure prophylaxis (PrEP) and continuation among adolescent girls and young women in the uMhlathuze Municipality, KwaZulu- Natal, South Africa*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Ms JJS Methazia

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220271

NAME: **(Principal Investigator)**	Ms JJS Methazia
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	*Factors associated with uptake of pre-exposure prophylaxis (PrEP) and continuation among adolescent girls and young women in the uMhlathuze Municipality, KwaZulu- Natal, South Africa*
DATE CONSIDERED:	2022/02/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor P Nyasulu
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/05/17

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **February** and therefore reports and re-certification will be due in the month of **February** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____