Improving Pre-exposure Prophylaxis (PrEP) delivery for HIV prevention among women of reproductive age in Sub-Saharan Africa

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a dissertation

submitted in partial fulfillment of the

requirement for the degree of

Doctor of Philosophy

University of Washington

2024

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Program Authorized to Offer Degree:

Public Health-Epidemiology

University of Washington

Abstract

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Adolescent girls and young women in East and Southern Africa are disproportionately affected by HIV. Tenofovir disoproxil fumarate (TDF)-based oral pre-exposure prophylaxis (PrEP) reduces the risk of HIV acquisition with consistent daily adherence and has been recommended for use since 2015 by the World Health Organization. However, for a multitude of reasons, young African women have difficulty adhering to daily pill-taking and/or accessing refills for oral PrEP. TDF-based oral PrEP is generally safe but has been linked with low levels of bone mineral density (BMD) loss. Research is needed to evaluate if the use of TDF-based oral PrEP during pregnancy exacerbates maternal bone mineral density loss. Further, drug level monitoring (accompanied by feedback) and data-driven adherence counseling are essential to supporting young women using PrEP. Novel tools such as point-of-care tenofovir (POC TFV) urine test may have a significant impact on improving PrEP adherence. In addition to research to optimize the use of daily oral PrEP, new products with longer-acting formulations have been proven efficacious and are nearing programmatic implementation. These products, including an injection and a vaginal ring, have the potential to overcome the challenges of daily adherence and curtail the high HIV burden among African women. By leveraging data from recent prospective cohort

studies, we aimed to contribute to global efforts to optimize PrEP delivery to young women through this dissertation.

Our first study leveraged data from women enrolled in a prospective cohort study evaluating the impact of concurrent TDF-based PrEP and DMPA on bone health in Kampala, Uganda. In a sub-study of women who became pregnant in that cohort, we evaluated the impact of TDF-based PrEP use on BMD loss during pregnancy. Secondarily, we investigated the effect of pregnancy on daily oral PrEP adherence and continuation. We observed significant BMD loss among pregnant women who were using PrEP, which was likely driven by pregnancy, rather than PrEP use. Our study also reported that women experiencing pregnancy were significantly less likely to use PrEP than women without a pregnancy through analyses comparing pregnant versus non-pregnant women and pregnant versus non-pregnant periods among women who become pregnant.

Our second study evaluates a recently developed and validated point-of-care urine tenofovir (POC TFV) test to determine whether its use improves the accuracy of self-reported adherence to pre-exposure prophylaxis (PrEP) and sexual behavior. We leveraged data from a prospective cohort of young women using TDF-based oral PrEP in Uganda. We observed that the introduction of a POC urine test for TFV substantially improved the accuracy of self-reported PrEP adherence. We also saw a moderate concordance between the POC urine TFV and TFV-DP in DBS, and greater reports of activities that are traditionally challenging to disclose to an HIV prevention counselor – condomless sex and low PrEP adherence – when the POC urine test was used. Further research is needed to evaluate the utility of POC urine TFV testing to monitor PrEP adherence and inform provider decision-making in clinic settings. However, our findings indicate that the POC urine TFV test could play an important role in PrEP adherence counseling,

particularly in a low-resource setting, since it is projected to be low-cost once available commercially.

Our third study evaluated preferences and willingness to use novel PrEP products (i.e., injectable cabotegravir and dapivirine vaginal ring) among oral PrEP-experienced and inexperienced Kenyan women accessing family planning clinics. We conducted a cross-sectional study among women seeking services at 12 family planning clinics. We found that an overwhelming number of participants preferred injectable PrEP and would like to switch from their current oral PrEP regimen to injectable PrEP if it were available to them. Among participants without prior PrEP experience, 74% preferred injectable PrEP, 19% preferred oral PrEP, and 4% preferred the vaginal ring. Among previous oral PrEP users, 82% preferred injectable PrEP, 16% preferred oral PrEP, and only 2% preferred the dapivirine vaginal ring. Our findings suggest that in this population of reproductive-age women in Kenya, adding injectable PrEP to the HIV prevention toolkit could potentially increase PrEP use and overall coverage of HIV prevention.

Together, the results presented in this dissertation provide insights that have the potential to impact the delivery of daily oral PrEP and plans for the delivery of novel PrEP products to young women in Eastern and Southern Africa. The findings of these studies will inform strategies to support PrEP adherence and continuation among women during pregnancy and the postpartum period, provide novel data on the use of POC TFV testing to support adherence counseling, and inform decisions on novel PrEP product provision for young African women. As newer PrEP products are nearing large-scale implementation, there is a need for making pregnant and adolescent girls, as well as young women, a priority population for these prevention methods, and committing to making these methods available, accessible, and affordable.

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ACKNOWLEDGMENTS

I am incredibly grateful to the many individuals who have made this work possible. First and foremost, my deepest gratitude goes to my dissertation committee: Renee Heffron, Deborah Donnell, Daniel Enquobahrie, Kenneth Mugwanya, and Nina Isoherranen. They have each spent countless hours generously sharing their time, energy, and expertise over the past five years. Special thanks to Renee, who dedicated numerous hours to brainstorming ideas, reviewing my manuscripts and proposals, guiding me through funding and scholarship applications, and much more. I thank Deborah Donnell for taking me under her wing as a research assistant at the beginning of my Ph.D. and introducing me to the world of PrEP and HIV research. I cannot thank Daniel Enquobahrie enough for being a constant source of support and inspiration. I thank Kenneth Mugwanya for providing me with numerous opportunities to contribute to remarkable projects. I am thankful to Nina Isoherranen for serving as my GSR and for the pharmacokinetic guidance she provided.

I would also like to express my sincere gratitude to all the women who participated in the Kampala Women's Bone Study and the Family Plus study. This work would not have been possible without their generous contribution to research. I thank the research teams in Kenya and Uganda for designing, leading, and implementing these studies. The International Clinical Research Center (ICRC) has been an incredible place to work and learn, and I am grateful to friends and colleagues at ICRC for their generous support over the past 5 years. Special thanks to Kathy Thomas, an amazing statistician with whom I have had the privilege of working and learning.

Finally, I would like to thank mentors, friends, and family who have supported me on this journey. Thank you to Dr. Arthur Sillah for being an incredible peer mentor and friend. Hiwot Zewdie, Hiwot Weldemariam, Adino Tsegaye, Mariama Bah, Tina Sesay, and Ramya Kumar have been incredible friends and inspiring epidemiologists. I am incredibly grateful to have crossed paths with you all during our Epidemiology PhD journey. To my Seattle family, Desta, Luel, Alazar, Ermias, Beti, and Hilan—I am grateful for your friendship and unwavering moral support. Special thank you to my Ethiopian UWC family, Dr. Yilkal Ayino, Sophia Ali, Banteaymolu Alebachew, Dr. Mesay Gebresilasse, and Mati Debela for being a source of comfort and incredible friendships. Lastly, my husband and best friend, Fikir Kibret, none of this would have been possible without your unconditional love, support, and selfless sacrifice. A special thank you to my little sunshine, Aman, for bringing so much joy and happiness into my life.

DEDICATION

For young women in Ethiopia and around the world affected by war and conflicts- your dreams matter

-AND-

To my parents Belay Zewdie and Mesay Abate for believing in my dreams

Chapter 1. Introduction

In 2022, adolescent girls and young women in sub-Saharan Africa accounted for more than 77% of all new HIV infections among young people aged 15-24 (1). Adolescent girls and young women (AGYW) are particularly vulnerable to HIV due to social, structural, behavioral as well as biological factors (2,3) that increase their susceptibility and exposure to HIV. Poverty, gender-based violence, and inadequate access to education increase young women's vulnerability to HIV (4,5). Pre-exposure prophylaxis (PrEP) provides a user-controlled option for young women to manage their own HIV risk.

Oral tenofovir (TDF) or TDF co-formulated with emtricitabine (TDF/FTC) based PrEP is a safe and effective method of HIV prevention for persons at high risk for HIV infection including pregnant women (6–10). TDF-based oral PrEP is highly effective in reducing the risk of HIV infection among women with consistent daily adherence (6,11). However, oral PrEP adherence and persistence have been low among young African women. Two early oral PrEP efficacy clinical trials conducted among African women failed to show efficacy against HIV infection mainly due to poor adherence to the study medications as measured by plasma tenofovir levels (8,12,13). Subsequent real-world studies have shown that the majority of users discontinue oral PrEP in the first 1 to 3 months (14,15). Reasons for PrEP discontinuation or low adherence cited by young women include side effects, pill burden, difficulty concealing pill-taking, negative consequences of inadvertent disclosure, and frequent visits to clinics (13,16–18). Thus, alternative PrEP products that require less frequent dosing, and offer greater discreetness are needed to address users' needs and preferences.

Currently, two long-acting PrEP products, the monthly dapivirine vaginal ring (DVR) and 2-monthly injectable cabotegravir (CAB-LA) have strong safety and effectiveness data among

African women (19–24). DVR reduced the risk of HIV by up to 56% and the World Health Organization currently recommends the use of DVR as an additional prevention option for women at substantial risk of HIV (25,26). CAB-LA was approved by The U.S. Food and Drug Administration (FDA) in 2021 and in a trial conducted in African women, 600mg CAB-LA as a single injection every 8 weeks was highly efficacious against HIV acquisition (19,27,28).

For young African women, pregnancy is a period with elevated risk for acquiring HIV (29–31), estimated to be 3-fold higher than non-pregnant periods (29,32). Maternal tenofovir use is not associated with adverse pregnancy, birth, and infant outcomes (33). The World Health Organization (WHO) guidelines recommend offering oral PrEP-containing TDF to HIV-negative pregnant and postpartum women at substantial risk of acquiring HIV (33–35). However, there are unanswered questions about the joint effect of TDF-based PrEP and pregnancy on maternal bone density. In addition, studies have shown that pregnant women struggle with PrEP use and adherence further evaluations are needed to understand the effect of pregnancy PrEP use and adherence.

Further, drug monitoring (accompanied by feedback) and data-driven adherence counseling are essential to supporting young women using PrEP (36–39). A point-of-care tenofovir (POC TFV) urine test is a novel method of adherence monitoring that may have a significant impact on improving PrEP adherence and encouraging open dialogue between clients and providers (40–42). The POC TFV urine test detects tenofovir concentration with high accuracy, is non-invasive, and can be performed by non-laboratory personnel in under five minutes (43). However, the influence of POC TFV tests as a component of PrEP adherence counseling in young African women has not been evaluated.

With this work, we utilized data collected from prospective cohorts of young women initiating PrEP to further our understanding of the effect of oral PrEP during pregnancy on maternal bone density, PrEP use, and adherence during pregnancy, user preferences of novel PrEP products, as well as the utility of POC TFV testing for adherence monitoring. Through these studies, we provide evidence that has the potential to impact the delivery of daily oral PrEP and plans for the delivery of novel PrEP products for young women in sub-Saharan Africa.

Chapter 2: The effect of daily oral PrEP use during pregnancy on bone mineral density among adolescent girls and young women in Uganda

Does TDF-based oral PrEP use during pregnancy exacerbate bone mineral density loss?

Tenofovir disoproxil fumarate (TDF)-based pre-exposure prophylaxis (PrEP) is currently the only PrEP product recommended for use during pregnancy for at-risk cisgender women. However, TDF-based PrEP has been linked with some bone mineral density loss. Pregnancy is also associated with bone mineral density loss. Peak bone mass is usually reached by the ages of 20 and 26 years and plateaus until menopause (12,13). The use of tenofovir-based PrEP during pregnancy by young women may yield detrimental changes to bone health which may increase the risk of osteoporosis and fractures in later life.

In Chapter 2, we examined the effect of TDF-based oral PrEP use during pregnancy on women's bone mineral density using data from a prospective cohort of young women from the Kampala Women's Bone Study. We found that BMD decline during pregnancy was not significantly greater among women who used PrEP during pregnancy compared to pregnant women with no PrEP exposure, suggesting that BMD loss in PrEP-using pregnant women is

largely driven by pregnancy rather than PrEP use. Our study has also shown that women who experienced pregnancy while using PrEP were less likely to adhere to or continue using PrEP than those who did not experience pregnancy. Taken together, further assessments of the effect of TDF-based PrEP use during pregnancy on bone health are needed. Additionally, it is important to advance research on alternative PrEP products that may have a lesser effect on bone health and could improve PrEP adherence during pregnancy

Chapter 3: A point-of-care tenofovir urine test improves accuracy of self-reported PrEP adherence and sexual behavior among young women

Oral PrEP requires consistent daily adherence and a complex array of social and structural factors make it harder for adolescent girls and young women to have the required PrEP adherence for HIV prevention (13,16–18). Data-driven adherence counseling using objective PrEP adherence could help improve adherence in people using PrEP (36–39). However, drug-level testing is not widely available in low-resource settings, therefore, there is a reliance on self-report to guide adherence counseling. Findings from a variety of research and implementation programs underscore challenges with self-reporting which is prone to over-reporting, recall, and social desirability bias. Accurate self-reported behavior could facilitate open discussions between providers and PrEP users about HIV risk and increase the opportunity for early intervention with adherence counseling, especially when PrEP use levels are less than optimal.

In Chapter 3, we evaluated a recently developed point-of-care urine tenofovir (POC TFV) test to determine whether its use improves the accuracy of self-reported PrEP adherence and influences reported sexual behavior by young African women. We observed that the introduction of a POC urine test for TFV substantially improved the accuracy of self-reported PrEP adherence. We also saw a moderate concordance between the POC urine TFV and TFV-DP in

DBS. In addition, we found that participants were more likely to report socially undesirable results such as engaging in condomless sex and having low PrEP adherence when the POC urine TFV test was used during their visit. Ours is one of the first studies to use the POC TFV test in a PrEP program among young women, showing the benefits of the assay.

Chapter 4: High preference for injectable pre-exposure prophylaxis among young women in Kenya

What type of PrEP product do young women prefer?

Oral PrEP was introduced in 2012 and since then nearly 6 million people worldwide have started using PrEP, but the uptake still falls short of the UNAIDS target of reaching 10 million people at substantial risk of HIV by 2025 (44,45). In additional to oral TDF-based PrEP, two longer-acting products, the dapivirine vaginal ring, and injectable cabotegravir have been approved for use by women, and a variety of other PrEP products are currently in development including short-acting, long-acting, and multipurpose prevention options. Providing young women with a variety of PrEP options in type and methods of delivery that best suit their circumstances and HIV prevention needs will increase PrEP coverage and its public health impact. As programs are preparing to launch delivery of these longer-acting products, it is important to understand users' needs and preferences.

In Chapter 4, we conducted a cross-sectional study among women seeking services at 12 family planning clinics in Kenya to understand preferences for and willingness to use newer PrEP products among participants who had previous experience using oral PrEP and those who did not. We found that an overwhelming number of users preferred injectable PrEP, followed by oral PrEP. We found that preference for the ring was relatively low compared to oral and injectable PrEP. Our findings suggest that in this population of reproductive-age women in Kenya, adding injectable PrEP to the HIV prevention toolkit could potentially increase PrEP use and overall coverage of HIV prevention. However, our study investigated hypothetical preferences, and participants were not required to use the products during the visit nor were novel products available to show participants. Hence, the actual product preference might differ

when individuals have a real choice in front of them. Future studies need to be conducted to assess the actual uptake of products and qualitatively explore the reasons behind product preferences.

Summary

This dissertation addresses safety concerns regarding oral PrEP use during pregnancy, novel methods that could be used to support oral PrEP use among young women, and the preparation for newer longer-acting PrEP modalities centering high-risk adolescent girls and young women in Kenya and Uganda. Our work provides evidence on the safety of oral PrEP use during pregnancy, novel data on the use of point-of-care TFV testing to support adherence counseling, and data to inform decisions on the delivery of longer-acting injectable cabotegravir and dapivirine ring products to young African women. Together, these results highlight some modalities to optimize HIV prevention among adolescent girls and young women in East Africa. We also highlighted the need for making pregnant and adolescent girls, as well as young women, a priority population for newer prevention methods and committing to making these methods available, accessible, and affordable.

Chapter 2**:** The effect of daily oral PrEP use during pregnancy on bone mineral density among adolescent girls and young women in Uganda

Published citation: Zewdie K, Kiweewa FM, Ssebuliba T, Morrison SA, Muwonge TR, Boyer J, Bambia F, Badaru J, Stein G, Mugwanya KK, Wyatt C, Yin MT, Mujugira A, Heffron R. The effect of daily oral PrEP use during pregnancy on bone mineral density among adolescent girls and young women in Uganda. *Front Reprod Health*. 2024 Jan 8;5:1240990. doi: 10.3389/frph.2023.1240990. PMID: 38260049; PMCID: PMC10801233

Title: The effect of daily oral PrEP use during pregnancy on bone mineral density among adolescent girls and young women in Uganda

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Keywords: Bone Mineral Density, Oral PrEP, Young women and adolescent girls, HIV prevention, Uganda

Abstract

Introduction: Oral pre-exposure prophylaxis (PrEP) is recommended during pregnancy for at-risk cisgender women. Pregnancy is known to impede bone growth and tenofovir-based PrEP may also yield detrimental changes to bone health. Thus, we evaluated the effect of PrEP use during pregnancy on bone mineral density (BMD).

Methods: We used data from a cohort of women who were sexually active, HIV-negative, ages 16-25 years, initiating DMPA or choosing condoms for contraception and enrolled in the Kampala Women's Bone Study. Women were followed quarterly with rapid testing for HIV and pregnancy, PrEP dispensation, and adherence counseling. Those who became pregnant were counseled on PrEP use during pregnancy per national guidelines. BMD of the neck of the hip, total hip, and lumbar spine was measured using dual-energy x-ray absorptiometry at baseline and annually. We compared the mean percent change in BMD from baseline to month 24.

Results: Among 499 women enrolled in the study, 105 pregnancies occurred in 90 women. At enrollment, the median age was 20 years (IQR: 19-21) and 89% initiated PrEP. During pregnancy, 67% of women continued using PrEP and PrEP was dispensed in 64% of visits. BMD declined significantly in women using PrEP during pregnancy compared to women who were not pregnant nor used PrEP: relative BMD change was -2.26% (95% CI: -4.63 to 0.11, p=0.06) in the femoral neck, -2.57 % (95% CI: -4.48 to -0.66, p=0.01) in total hip, -3.06 % (95% CI: -5.49 to -0.63, p=0.001) lumbar spine. There was no significant difference in BMD loss when comparing PrEP-exposed pregnant women to pregnant women who never used PrEP. Women who became pregnant were less likely to continue PrEP at subsequent study visits than women who did not become pregnant (adjOR: 0.25, 95% CI: 0.16-0.37, p<0.001). Based on pill counts, there was a 62% reduction in the odds of high PrEP adherence during pregnancy (adjOR=0.38, 95% CI: 0.27-0.58, p<0.001).

Conclusion: Women who used PrEP during pregnancy experienced a similar reduction in BMD as pregnant women with no PrEP exposure, indicating that BMD loss in PrEP-using pregnant women is largely driven by pregnancy and not PrEP.

Introduction

Pregnancy is a period with an elevated risk for acquiring HIV (29–31), estimated to be >2-fold higher than non-pregnant periods (29,32). Biological changes in hormonal levels as well as changes in sexual behavior are likely responsible for the increase in HIV susceptibility of cisgender women during pregnancy (46,47). Pregnancy rates in sub-Saharan Africa are among the highest in the world and oral PrEP can play a critical role in reducing HIV acquisition during this period (48,49). Oral PrEP containing tenofovir disoproxil fumarate (TDF) is safe and recommended for use during pregnancy and postpartum by women at substantial risk of acquiring HIV (33–35).

With reassuring data on the safety of PrEP with regards to birth outcomes and infant growth (35), the remaining questions are related to whether there are subclinical consequences from PrEP use during pregnancy, such as effects on bone health. Women's bone mineral density (BMD) reaches its peak between the ages of 20 and 26 years and plateaus until menopause (50,51). However, BMD loss or premature attainment of peak BMD can occur in premenopausal women due to various reasons, including the use of depot medroxyprogesterone acetate (DMPA), pregnancy, and breastfeeding (50). Changes in BMD during pregnancy and lactation are due to mineral transfer to a fetus or infant to facilitate growth (50,52). Additionally, the use of TDF-based oral PrEP has been postulated to be a potential factor linked to BMD loss (53,54) because of its excretion through the renal system and the kidney-bone development pathway (55,56). Despite the independent association of pregnancy and BMD and the subclinical impact of TDF on creatinine levels, it is not known whether PrEP use during pregnancy and/or breastfeeding could exacerbate BMD loss in young women.

In addition, how pregnancy impacts oral PrEP adherence and continuation needs to be further evaluated. A recent PrEP implementation study among pregnant women found that only

40% continued PrEP use one month after initiation (57). While protecting the fetus from HIV might provide an incentive for pregnant women to use and adhere to PrEP, experiencing side effects in conjunction with those elicited by pregnancy and fear of unknown effects on the fetus might prompt discontinuation, beyond the effects of stigma and pill burden that all PrEP users face (57–61). Prior studies have primarily examined patterns of PrEP use among women who initiated PrEP use during pregnancy; however, PrEP use patterns may differ in women who were already on PrEP at the time of pregnancy.

Using data from women enrolled in a prospective cohort study evaluating the impact of concurrent TDF-based PrEP and DMPA on bone health in Kampala, Uganda, we evaluated the impact of TDF-based PrEP use on BMD loss during pregnancy. Secondarily, we investigated the effect of pregnancy on daily oral PrEP adherence and continuation.

Methods

Study design and population: We used data from all women enrolled in the Kampala Women's Bone Study (ClinicalTrials.gov #NCT03464266), an open-label prospective cohort study aimed to address bone safety questions with concurrent TDF-based PrEP and DMPA use. Between May 2018 and March 2020, the Kampala Women's Bone Study recruited women who were at high risk for HIV and seeking DMPA or condoms as contraception in family planning clinics, youth-based centers, and higher learning institutions in Kampala, Uganda. Women who were HIV-negative, ages 16-25 years, initiating DMPA or choosing to use male condoms for contraception, without contraindications for DMPA or TDF-based PrEP, and not planning to become pregnant in the next 24 months were eligible to enroll in the study.

Data collection and outcomes:

Over 24 months, women were followed quarterly with HIV prevention counseling and condom distribution, diagnostic testing for HIV (using rapid testing according to the national algorithm), urine pregnancy testing, provision of DMPA injections, offers of PrEP, PrEP adherence counseling, and provision of PrEP medication (FTC/ TDF). At enrollment and quarterly visits, interviewers administered standardized questionnaires to collect data on demographic characteristics, medical history, sexual behavior, sexual relationship power, HIV perception and salience, diet and physical activity, alcohol and drug use, and contraceptive and PrEP use. At the first visit at which the participant was found to be pregnant, data on the last menstrual period date, expected delivery date, whether the pregnancy was intended, obstetric history, and decision on PrEP continuation were collected. Women who became pregnant while using PrEP were counseled about the known and unknown risks and benefits of PrEP use during pregnancy according to the national guidelines and supported to continue or discontinue PrEP.

At enrollment and annual study visits, after confirming HCG negative urine pregnancy test results, dual-energy x-ray absorptiometry (DXA) scans were conducted to measure BMD for the lumbar spine, total hip, and neck of the hip. For women who were pregnant, DXA scans were withheld and completed as soon after pregnancy as possible. We measured PrEP continuation using pharmacy PrEP refill data and pill count as measures of PrEP adherence and defined "continuation" based on PrEP being dispensed at the visit. Quarterly pill use was quantified by dividing the number of pills used and pills not returned by the expected number of pills to be used, and a value of ≥80% was considered high adherence. The start of pregnancy was estimated using the last menstrual period date or the estimated delivery dates. The end of pregnancy was determined using the reported date of pregnancy outcome or estimated delivery date.

Statistical Analysis:

Baseline participant characteristics were summarized using descriptive statistics. To evaluate the effect of PrEP use during pregnancy on BMD, we used a generalized linear model (GLM) with a Gaussian link to compare the mean percent change in BMD between baseline and the end of the two-year follow-up in women who were using PrEP during pregnancy and non-pregnant women who didn't initiate PrEP during the study. Models were adjusted for confounders identified *a priori*: age as a continuous variable, baseline body-mass index (BMI), and baseline DMPA use. In a sensitivity analysis, we repeated the analysis excluding non-full-term pregnancies. To evaluate the effect of pregnancy on PrEP continuation and PrEP adherence, we used generalized estimation equation (GEE) models with a logit-link and exchangeable correlation structure to compare the odds of PrEP continuation and PrEP adherence between women who experience pregnancy and those who did not experience pregnancy over the 24 months study follow up. The models were adjusted for potential confounders identified *a priori*: age, education, income, relationship status, and partner's HIV status. In separate models, we compared PrEP continuation during pregnancy to non-pregnant periods among women who became pregnant during the study. All analyses were done using R 4.0.

Ethical considerations

The study protocol was approved by the National HIV/AIDS Research Committee of Uganda, the Uganda National Council for Science and Technology, and the Human Subjects Division at the University of Washington. Participants ≥18 years provided written informed consent and participants <18 years provided written assent with a consenting guardian or were qualified to provide consent based on their status as an emancipated or mature minor.

Results:

Participant characteristics

A total of 499 sexually active young women were enrolled in the study. At enrollment, the median age was 20 years [interquartile range (IQR):19-21], 87 were married or had a steady partner, 92% received financial support from their partners, 63% did not know their partner's HIV status, and 89% initiated PrEP. Over the 24-month study period, 90 participants became pregnant. Women who became pregnant more frequently had chosen to use condoms than DMPA at baseline as a contraceptive compared to women who did not become pregnant (61% versus 43%, respectively). Other baseline characteristics including age, marital status, education level, sexual behavior characteristics, BMI, and BMD were similar between women who did and did not become pregnant (Table 1).

Pregnancy characteristics:

Among 499 participants enrolled in the study, 396 (79%) were retained for one year, and 331 (66%) participants were followed for two years. Although we were not able to contact the majority (60%) of participants who were lost to follow-up to ascertain reasons for study discontinuation, two-thirds of the loss to follow-up occurred after March 2020, when the COVID-19 pandemic began in Uganda. During the study period, 105 pregnancies occurred, including 15 women who experienced multiple pregnancies. The median time between enrolment and the start of pregnancy was 426 days (IQR: 235-524). Among those who became pregnant, 61 (67%) women (during 72 [69%] pregnancies) used PrEP during their pregnancy (Table 2). Overall, 73% of pregnancies were unintended, 62% were the woman's first pregnancy, and 35% of pregnancies resulted in pregnancy loss. There was no difference in pregnancy outcomes by PrEP exposure groups.

Association of PrEP use, pregnancy, and bone mineral density

We examined the association between PrEP use during pregnancy with changes in mean BMD from baseline to 2 years at the neck of the hip, lumbar spine, and total spine. Among the 331 study participants who were followed for two years, 294 (89%) participants had DXA scans at baseline and the 24-month visit. The median time between the end of pregnancy and the exit DXA scan was 119 days [IQR: 55-221]. The mean percent change in BMD for pregnant women who used PrEP during pregnancy at the neck of the hip was -1.91% (95% CI: -4.28% to +0.46%), -2.20% (95% CI: -4.17% to - 0.23%) at the total hip and -3.78% (95% CI: -6.28% to -1.27%) at the lumbar spine [Table 3]. Over the 24-month study period, the mean percent change in BMD was significantly greater in pregnant women using PrEP during pregnancy relative to women who were not exposed to either PrEP or pregnancy. After adjusting for age, BMI, and DMPA use prior to pregnancy, the relative mean percent change in BMD was -2.26% (95% CI: -4.63 to 0.11, p=0.06) at the femoral neck, -2.57 % (95% CI: -4.48 to -0.66, p=0.01) at the total hip, and -3.06 % (95% CI: -5.49 to -0.63, p=0.001) at the lumbar spine. The decline in BMD in those pregnant but who had never been exposed to PrEP or who were pregnant but not taking PrEP during pregnancy was not significantly different compared to women who were not pregnant and had never been on PrEP, although numbers were small in both groups.

BMD declined significantly in pregnant women who used PrEP during pregnancy compared to women who used PrEP but did not become pregnant. After adjusting for age, BMI, and DMPA use, the relative mean BMD percent change was -2.47% (95% CI: -4.22 to – 0.71, p=0.006) at the femoral neck, -2.08 % (95% CI: -3.50 to -0.66, p=0.004) at the total hip, and -2.98 % (95% CI: -4.78 to -1.18, p=0.001) at the lumbar spine. The decline in BMD in pregnant women who were using PrEP during pregnancy was not statistically significant compared to women who

experienced pregnancy but were not exposed to PrEP. The relative mean BMD percent change was -2.26% (95% CI: -6.54 to 2.01, p=0.30) at the femoral neck, -2.47 % (95% CI: -5.92 to 0.99, p=0.16) at the total hip, and 0.67% (95% CI: -3.71 to -5.06, p=0.76) at the lumbar spine. Similar results were observed in a sensitivity analysis limited to full-term pregnancies.

PrEP continuation during pregnancy:

Among the 90 women who became pregnant during the study, 10 (11%) did not use PrEP during the study, 19 (21%) did not continue PrEP use during pregnancy, and 61 (67%) chose to continue PrEP during their pregnancy. Among 80 women who became pregnant after initiating PrEP, PrEP was dispensed in 64% of visits during pregnancy (Table 4).

After adjusting for age, education, relationship status, income, and partner's HIV status, we found that women who became pregnant were less likely to get PrEP refill at subsequent study visits than women who did not become pregnant (adjusted OR: 0.25, 95% CI: 0.17, 0.37, p <0.001). In the subset of women who became pregnant and had initiated PrEP (N=80), there was a statistically significant 70% reduction in the odds of PrEP continuation during pregnancy (adjusted OR=0.30, 95% CI 0.20-0.46 p<0.001) compared to their non-pregnant periods.

PrEP Adherence:

Over the 24-month follow-up period, there were 2,735 follow-up study visits among participants who were dispensed PrEP at a previous visit. Based on pill counts, high PrEP adherence (>80% of expected pills not returned) was reported in 69% of follow-up visits. After adjusting for age, education, relationship status, income, and partner's HIV status, women had 62% reduced odds

of high PrEP adherence (adjOR 0.38; 95% CI 0.27-0.58, p<0.001) during pregnancy compared to non-pregnant periods.

Discussion

In this study in Uganda with young women who initiated PrEP before pregnancy, we observed significant BMD loss among pregnant women using PrEP that was likely driven by pregnancy, rather than PrEP use. Our study also reported that women experiencing pregnancy were significantly less likely to use PrEP than women without a pregnancy through analyses of pregnant versus non-pregnant women and pregnant and non-pregnant periods among women who become pregnant. Additionally, we found that women are less likely to be adherent to PrEP during pregnancy based on pill count data.

Over the two-year follow-up period, we observed a significantly greater loss in BMD among PrEP-exposed pregnant women compared to women who did not become pregnant and were not exposed to PrEP. Isolating our analysis to estimate the effect of PrEP only, we did not see a significant difference in BMD loss when comparing PrEP-exposed pregnant women to pregnant women who never used PrEP. However, it is important to note that in both the femur and the hip, we saw a trend toward a greater reduction in BMD in women who use PrEP during pregnancy, and due to the small sample size of pregnant women who are not exposed to PrEP our estimates may be unstable. Given that previous studies have shown that TDF-based PrEP is associated with bone loss (54,62,63) and our study included young women who have not yet achieved peak bone mass, have high fertility rates, and are more likely to be exposed to injectable contraceptives that may compound bone loss (64), any significant BMD reduction in this group is particularly concerning and warrants further investigation. Studies are needed to determine the clinical implications of the decline in BMD associated with concurrent pregnancy

and high adherence to TDF-based PrEP in young women and whether the decline is reversible after the end of pregnancy. It is also important to study the potential implications of a more prolonged decline in BMD when TDF-based oral PrEP is used during breastfeeding and the trajectory of BMD subsequent to the cessation of lactation.

Among the 80 women who initiated PrEP and became pregnant, 61(76%) chose to continue PrEP during pregnancy. However, our results indicate at subsequent visits, pregnant women were less likely to get PrEP refills compared to non-pregnant women, highlighting the importance of open discussion about the risks and benefits of PrEP use during pregnancy, the increased risk of HIV acquisition and devising strategies to support prevention-effective PrEP use in adolescent girls and young women during pregnancy. A recent study in South Africa found that the most common reason for PrEP discontinuation among pregnant women was gastrointestinal side effects, including nausea and vomiting (65). Providing women with counseling and strategies to manage nausea and vomiting could improve PrEP continuation. In addition, strategies such as regular adherence counseling, drug-level feedback, and adherence support clubs could be used to support oral PrEP adherence in young pregnant women (66–68).

Research in family planning methods has demonstrated that increasing the number of contraceptive products yielded increases in uptake and protection from unintended pregnancy (69,70). New PrEP products, particularly longer-acting PrEP, could reduce challenges with oral PrEP persistence and adherence and may be convenient for some women to use. Newer PrEP products may also have less effect on bone density, making them a good alternative for women worried about BMD loss during pregnancy. However, safety data on the use of these products by pregnant and breastfeeding women are still forthcoming and the current product labels exclude their use by these populations.

We acknowledge that our study has several limitations. First, we used pill count as a measure of adherence which might not accurately reflect whether participants adhere to PrEP or not. Adherence measured using pill counts does not always align with TFV levels measured using pharmacologic adherence measures such as plasma and dried blood spots (DBS) (8,12,71,72). However, pharmacologic methods require skilled laboratory personnel and specialized equipment, making them difficult to access in resource-limited settings such as Uganda (37). A point-of-care TFV (POC TFV) urine test could be used for data-driven adherence counseling to support young women using PrEP (40–42). Future studies are planned to evaluate PrEP exposure using POC TFV(73). Even with these limitations, PrEP adherence was relatively poor during pregnancy in our study population, and future studies should evaluate the impact of more consistent TDF-based PrEP exposure on BMD decline during pregnancy. Second, we used DXA scans at enrollment and exit from the study. For some women, the exit DXA scan closely followed the end of pregnancy while for others the length of time between pregnancy and the DXA scan was longer. BMD begins to rebound after pregnancy and continues to rebound after breastfeeding ceases and thus, the longer the interval between the end of pregnancy and the exit DXA scan, the greater the potential for lactation to confound the relationship between PrEP, pregnancy, and BMD since most women in Uganda aim to breastfeed for 2 years. Our data on breastfeeding were insufficient to accurately account for the effect of lactation. Additionally, our analysis did not account for the length of PrEP exposure during pregnancy. The extent of bone loss could be different between those with longer-term PrEP exposure compared to women with shorter-term PrEP exposure.

Conclusions

In conclusion, we found that BMD decline during pregnancy was not significantly greater among women who used PrEP during pregnancy compared to pregnant women with no PrEP exposure, suggesting that BMD loss in PrEP-using pregnant women is largely driven by pregnancy rather than PrEP use. Our study has also shown that women who experienced pregnancy while using PrEP were less likely to adhere to or continue using PrEP than those who did not experience pregnancy. Taken together, further assessments of the effect of quantifiable TDF-based PrEP use during pregnancy on bone health are needed. Additionally, it is important to advance research on alternative PrEP products that may have a lesser effect on bone health and could improve PrEP adherence during pregnancy.

Competing interests

All authors declare no competing interests.

Authors' contributions

Study conceptualization: KZ and RH. Data analysis: KZ. Writing – original draft: KZ and RH. Writing – review and editing: All authors. All authors participated in the critical review and have read and approved the final manuscript.

Acknowledgments

Our sincere gratitude goes to the women who participated in this study for generously giving their time, samples, and information to the study team. We are also grateful to the study team members and our collaborative partners in Uganda and the US who helped to make this study possible. The study was funded by the Eunice K. Shriver National Institute for Child Health and Human Development (R01HD089843) and FTC/TDF medication was donated by Gilead Sciences LLC. KZ was supported by the University of Washington STD/AIDS Research Training Grant

Tables

Table 1: Baseline characteristics of women in in the study (N=499)

Characteristic	No pregnancy during study, N = 409, N (%) or median (IQR)	At least one pregnant during study follow-up, N = 90 N (%) or median (IQR)	Total, N=499 N (%) or median (IQR)
Age (years)	20 (19, 21)	20 (18, 21)	20 (19, 21)
Relationship status			
Single	48 (12%)	17 (19%)	65 (13%)
Married/in a steady partnership	361 (88%)	73 (81%)	434 (87%)
Lives with partner	22 (5.4%)	2(2.2%)	24 (4.8%)
Earns own income	211 (52%)	50 (56%)	261 (52%)
Partner provides financial support	377 (92%)	80 (89%)	457 (92%)
Years of education	11(8, 12)	11 (9, 12)	11 (8, 12)
Partners HIV status			
Positive	7 (1.7%)	2 (2.2%)	9 (1.8%)
Negative	147 (36%)	30 (33%)	177 (36%)
Unknown	254 (62%)	58 (64%)	312 (63%)
Travel time to research clinic			
<1 hour	58 (14%)	18 (20%)	76 (15%)
1-2 hours	335 (82%)	68 (76%)	403 (81%)
>2 hours	16 (3.9%)	4 (4.4%)	20 (4.0%)
Any condomless sex, past 3 months	274 (67%)	63 (70%)	337 (68%)
Any condomless sex, past 7 days	123 (49%)	23 (47%)	146 (48%)
Had more than one partner, past 3 months	238 (58%)	41 (46%)	279 (56%)
Contraception choice			
Condoms	176 (43%)	55 (61%)	231 (46%)
DMPA	233 (57%)	35 (39%)	268 (54%)
Initiated PrEP	360 (88%)	80 (89%)	431 (86%)
Body-mass index, kg/m²	23 (21, 25)	23 (21, 25)	22 (21, 25)
Mean BMD (g/cm2)			
The neck of the hip	0.86 (0.11)	0.87 (0.12)	0.85 (0.11)
Lumbar spine	0.95 (0.12)	0.95 (0.12)	0.93 (0.11)
Total hip	0.94 (0.10)	0.94 (0.10)	0.93 (0.09)

Table 2: Pregnancy characteristics

Characteristic	Overall, N = 105, n (%)	Used PrEP during pregnancy	
		No, N = 33, n (%)	Yes, N = 72, n (%)
Pregnancy was intended*			
No	77 (73%)	19 (58%)	58 (81%)
Yes	28 (27%)	14 (42%)	14 (19%)
Number of previous pregnancies			
None	65 (62%)	20 (61%)	45 (62%)
One	33 (31%)	11 (33 %)	22 (31%)
More than one	7 (7%)	2 (6%)	5 (7%)
Pregnancy outcome:			
Live birth	40 (38%)	12 (38%)	28 (42%)
Premature live birth	3 (3.0%)	0 (0%)	3 (4%)
Pregnancy loss	37 (35%)	12 (38%)	25 (37%)
Unknown	25 (24%)	9 (27%)	16 (22%)

*Ascertained through interviewer conversation with the participant

Table 3: Adjusted difference in the mean BMD at the neck of the hip, lumbar spine, and total hip

			Comparisons to women who never pregnant and never used PrEP		Comparisons of the impact of pregnancy among women who used PrEP		Comparisons of the impact of PrEP among women who experienced pregnancy	
	N=294	**% Change in BMD from baseline (g/cm2)**	**Adjusted difference in % change in BMD (95% CI) ***	**p-value**	**Adjusted difference in % change in BMD (95% CI) ***	**p-value**	**Adjusted difference in % change in BMD (95% CI) ***	**p-value**
The neck of the hip (g/cm2)								
Not pregnant and no PrEP use ever	31	0.12 (-1.64, 1.89)	Ref.		---		---	
Not pregnant and used PrEP	206	0.54 (-1.35, 2.44)	0.21 (-1.75, 2.16)	0.83	Ref.		---	
Pregnant, no PrEP ever	6	-0.08 (-4.47, 4.31)	0.01 (-4.33, 4.33)	0.99	---		Ref	
Pregnant, no PrEP during pregnancy	12	-1.82 (-5.17, 1.53)	-1.59 (-5.03, 1.84)	0.36	---		---	
Pregnant and PrEP use during pregnancy	39	-1.91 (-4.28, 0.46)	-2.26 (-4.63, 0.11)	0.06	-2.47 (-4.22, -0.71)	0.006	-2.26 (-6.54, 2.01)	0.30
Total hip (g/cm2)								
Not pregnant and no PrEP use ever	31	1.01 (-0.45, 2.48)	Ref.		---		---	
Not pregnant and used PrEP	206	-0.14 (-1.72, 1.43)	-0.49 (-2.07, 1.09)	0.54	Ref.		---	
Pregnant, no PrEP ever	6	-0.08 (-3.73, 3.57)	-0.10 (-3.60, 3.39)	0.95	---		Ref.	
Pregnant, no PrEP during pregnancy	12	-0.69 (-3.44, 2.13)	-0.78 (-3.55, 2.00)	0.58	---		---	
Pregnant and PrEP during pregnancy	39	-2.20 (-4.17, -0.23)	-2.57 (-4.48, -0.66)	0.01	-2.08 (-3.50, -0.66)	0.004	-2.47 (-5.92, 0.99)	0.16
Lumbar spine (g/cm2)								
Not pregnant and no PrEP use ever	31	3.09 (1.22, 4.96)	Ref.		---		---	
Not pregnant and used PrEP	206	-0.50 (-2.50, 1.49)	-0.08 (-2.09, 1.92)	0.95	Ref.		----	
Pregnant, no PrEP ever	6	-4.05 (-8.68, 0.58)	-3.73 (-8.17, 0.76)	0.11	---		Ref.	
Pregnant, no PrEP during pregnancy	12	-1.75 (-5.28, 1.78)	-0.32 (-3.85, 3.20)	0.60	---		---	
Pregnant and PrEP use during pregnancy	39	-3.78 (-6.28, -1.27)	-3.06 (-5.49, -0.63)	0.01	-2.98 (-4.78, -1.18)	0.001	0.67 (-3.71, 5.06)	0.76

*Adjusted for age, BMI and DMPA use at enrollment.

Table 4: The association between PrEP continuation and pregnancy

	PrEP was not dispensed	**PrEP dispensed**	**Unadjusted analysis**		**Adjusted analysis ***	
PrEP continuation among pregnant and non-pregnant women in the study						
	Total Visits N=443, N (%)	Total Visits, N=3038, N (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
Pregnant	49 (36%)	87 (64%)	0.32 (0.22-0.46)	<0.001	0.25 (0.17-0.37)	<0.001
Not pregnant	394 (11%)	2,951 (88%)	Ref.	Ref.	Ref.	Ref.
PrEP continuation among women who became pregnant during pregnant and non-pregnant periods						
	Total Visits, N=147, N (%)	**Total Visits, N=565, N (%)**				
Pregnant	49 (36%)	87 (64%)	0.38 (0.26-0.56)	<0.001	0.30 (0.20-0.46)	<0.001
Not pregnant	98 (18%)	447 (82%)	Ref.	Ref.	Ref.	Ref.

*Adjusted for age, income, education, partner's HIV status, and relationship status

Table 5: Association of PrEP adherence with pregnancy

	High PrEP adherence	**Low PrEP Adherence**	**Unadjusted analysis**		**Adjusted analysis ***	
	Total Visits N=1,878 (N %)	Total Visits, N=857 (N %)	OR (95% CI)	p-value	OR (95% CI)	p-value
Pregnant	46 (44%)	58 (56%)	0.36 (0.25-0.54)	<0.001	0.38 (0.27-0.58)	<0.001
Not pregnant	1,832 (70%)	799 (30%)	Ref.	Ref.	Ref.	Ref.

*Adjusted for age, income, education, partner's HIV status, and relationship status

Chapter 3**:** A point-of-care tenofovir urine test improves accuracy of self-reported PrEP adherence and sexual behavior among young women

Title: A point-of-care tenofovir urine test improves accuracy of self-reported PrEP adherence and sexual behavior among young women

Short title: POC TFV urine test and self-reported adherence

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Funding: The study was funded by the Eunice K. Shriver National Institute for Child Health and Human Development (R01HD089843), and FTC/TDF medication was donated by Gilead Sciences LLC. KZ was supported by a University of Washington STD/AIDS Research Training Grant (T32 AI07140).

Abstract

Objectives: We evaluated a recently developed and validated point-of-care urine tenofovir (POC TFV) test to determine whether its use improves the accuracy of self-reported adherence to pre-exposure prophylaxis (PrEP) and sexual behavior.

Design: We enrolled sexually active HIV-negative women ages 16-25 years in Kampala, Uganda.

Methods: Women were followed quarterly for 24 months with HIV prevention counseling, PrEP dispensation, and adherence counseling. Midway through the study, the POC TFV test was introduced as part of routine study procedures. We examined changes in self-reported PrEP adherence, sexual behavior, and accuracy of self-reported PrEP adherence before and after the introduction of the POC TFV test.

Results: A total of 146 women receiving PrEP refills had ≥1 visit with a POC TFV test administered before the study exit. At baseline, the median age was 19 years (interquartile range [IQR]: 18-21) and the majority (76%) reported having condomless sex within the last three months. Participants more frequently self-reported low PrEP adherence (OR: 2.96, 95% confidence interval [CI]: 1.89-4.67, p=0.001) and condomless sex (OR: 1.47, 95% CI: 1.04-2.06, p=0.03) during visits using the test compared to visits without the test. The accuracy of self-reported PrEP adherence (determined by concordance with TFV-diphosphate levels) was greater when the test was used (61% versus 24%, OR: 4.86, 95% CI: 2.85-8.30, p<0.001).

Conclusions: When the POC TFV test was used, we observed greater reporting of condomless sex, low PrEP adherence, and more accurate reports of PrEP adherence. The test could facilitate honest conversations between clients and providers and warrant further investigation.

Keywords: Point-of-care tenofovir test, Young women, tenofovir, Oral PrEP, Self-report, Sexual behavior, PrEP Adherence

Introduction

Young women living in sub-Saharan Africa, particularly those aged <25 years, continue to experience one of the highest HIV incidence rates worldwide, with rates reaching 7% per year in some clinical trial populations (74,75). Tenofovir-based oral pre-exposure prophylaxis (PrEP) is a highly effective user-controlled HIV prevention method (6–10) and PrEP initiation has been met with enthusiasm by young African women (66). Still, PrEP adherence and continuation have been low, often with >50% discontinuing in the first few months of demonstration and programmatic implementation projects (57,68,76–78). Novel strategies to support women with oral PrEP adherence are needed.

Drug-level monitoring accompanied by feedback and data-driven adherence counseling could help improve PrEP adherence in young women using PrEP (36–39) by demonstrating the presence or absence of TFV systemically, facilitating conversations about barriers and facilitators to PrEP use. The utility of drug-level feedback has not been evaluated extensively among young African women. A recently completed trial (HPTN 082) evaluating drug-level feedback and PrEP adherence found that drug-level feedback was not associated with improved PrEP adherence in this demographic in the context of numerous behavioral and structural adherence interventions (66). However, the study used dried blood spots (DBS) to quantify intracellular tenofovir-diphosphate (TFV-DP) levels, and the feedback to women took place approximately two months after blood draws due to laboratory and operational requirements. Other available methods for monitoring pharmacologic adherence include the measurement of tenofovir (TFV), the active metabolite of tenofovir disoproxil fumarate (TDF), in plasma, peripheral blood mononuclear cells (PBMCs), and hair (79–81). Although these objective pharmacologic assays are used to quantify short and long-term drug exposure, they require skilled laboratory personnel and specialized

equipment, resulting in long turnaround times and high costs (37). A point-of-care tenofovir (POC TFV) urine test has recently been developed after identifying a highly selective antibody for TFV by the University of California, San Francisco (UCSF) and Abbott Diagnostics®. The POC TFV assay provides a novel method of real-time adherence monitoring and can measure recent (1-4 days) PrEP adherence within five minutes, allowing for actionable information in a clinic setting (40–42). This urine immunoassay can detect TFV concentrations in urine with 96% sensitivity and 100% specificity compared to the gold standard method of analyzing TFV levels in urine using liquid chromatography-tandem mass spectrometry (40–43). The POC TFV assay takes <5 minutes to run and costs <$2 per test, making it potentially suitable for use in routine clinical visits and in low-resource settings (41).

Individuals' risk for HIV can vary over time and high PrEP adherence is required during seasons of high risk to reap its prevention benefits (82). Real-time PrEP adherence monitoring can be used to validate the presence of TFV when PrEP is taken and may encourage more accurate sexual behavior reporting and an open dialogue between clients and providers (36–38). We evaluated the POC TFV assay as a component of PrEP adherence counseling to determine whether it improves self-reported PrEP use and sexual behavior reporting in young African women.

Methods

Study design and subjects: We used data from the Kampala Women's Bone Study (ClinicalTrials.gov #NCT03464266), a two-year open-label prospective cohort study aimed to address safety questions with concurrent use of TDF-based PrEP and depot medroxyprogesterone acetate (DMPA). HIV-negative, PrEP-eligible women, ages 16-25 years, initiating DMPA for the

first time or choosing to use male condoms for contraception in family planning clinics, youth-based centers, and higher learning institutions in Kampala, Uganda, were eligible for the study.

Data collection

Over 24 months, women were followed quarterly with HIV prevention counseling and condom distribution, diagnostic testing for HIV (using rapid testing according to the national algorithm) and urine pregnancy testing, provision of DMPA injections, PrEP adherence counseling, and provision of PrEP medication. At enrollment and quarterly visits, interviewers administered standardized questionnaires to collect data on demographic characteristics, sexual behavior, HIV perception and salience, and PrEP use. Women who became pregnant while using PrEP were counseled about the known and unknown risks and benefits of PrEP use during pregnancy according to the national guidelines and supported to continue or discontinue PrEP per their preference.

Description of the intervention and outcomes

POC urine test: The POC urine lateral flow assay that detects TFV was available for use midway into the study. Active study participants who had visits in months 9, 12, 21, and 24 received the POC urine test as a routine study procedure performed by a counselor who also documented sexual behavior. The POC urine TFV test provides a qualitative result indicating whether or not TFV with a concentration ≥1500 ng/mL was detected (indicating recent use) (41). To conduct the test, study participants self-collected urine samples using sterile cups, and the research staff performed the POC urine test. The results were then utilized to provide feedback to participants about their TFV detection and to inform adherence counseling.

PrEP adherence and accuracy of self-report: We used self-reported PrEP use, pill counts, and TFV-DP quantification in DBS (a well-characterized objective measure of TFV use) to characterize adherence (81). Participants were asked about their PrEP use in the past month with the question, "In the past month, how often did you take PrEP?" Those who reported taking PrEP "most of the time" or "all of the time" in the past month were categorized as having high PrEP adherence by self-report. We defined adherence by pill count by dividing the number of reported pills taken by the expected number of pills that should have been taken for daily use during the elapsed days and a value ≥80% was considered indicative of high adherence. We categorized adherence by DBS as either "detected" or "not detected". We defined accurate self-reported PrEP use at a visit if (a) the participant had high PrEP adherence by self-report and detectable levels of TFV-DP in DBS at the visit; or, (b) the participant did not have high PrEP adherence by self-report and had undetectable levels of TFV-DP in DBS at the visit.

Sexual behavior: We used the frequency of sex (vaginal or anal) without a condom in the past 7 days, and the frequency of sex without a condom in the past three months to measure changes in sexual behavior reporting.

Statistics

We summarized baseline demographic participant characteristics using descriptive statistics, with medians and interquartile ranges (IQR) for continuous variables and frequencies and proportions for categorical variables. We compared the agreement between adherence measured at the same visit by POC urine test and 1) self-report, 2) pill count, and 3) TFV-DP detection in DBS by using Kappa statistics. Next, we examined increases in self-reported condomless sex and PrEP non-adherence, behaviors that are complicated to disclose truthfully and often underreported, and the accuracy of self-reported PrEP adherence with the introduction of the POC urine test. We

compared the first visit with the POC urine test to a previous visit within a six-month period (when POC TFV tests were not used) using a generalized estimated equation (GEE) logistic regression model with an independent correlation structure.

Ethical considerations

The study protocol was approved by the National HIV/AIDS Research Committee of Uganda (ARC 202), the Uganda National Council for Science and Technology (SS 4505) and the Human Subjects Division at the University of Washington (STUDY00001451). Participants ≥18 years provided written informed consent, and participants <18 years provided written assent with a consenting guardian or were qualified to provide consent based on their status as an emancipated or mature minor.

Results

The Kampala Women's Bone Study (KWBS) enrolled 499 women from May 2018 to April 2020, and 432 women initiated PrEP (83). By the time of the urine POC TFV test introduction, participants had accrued 75% of the total follow-up time, and 118 participants had already exited the study. Of the remaining participants, 146 women who were on PrEP had at least one visit with a POC urine test before the end of their 24-month follow-up period. Of these 146, the median age was 19 years (interquartile range (IQR): 18 - 21), 88% were either married or in a steady partnership, 68% had partner(s) with an unknown HIV status, the majority (76%) reported engaging in condomless sex within the last 3 months, and 68% of participants reported having multiple partners (Table 1). These characteristics are similar to participants enrolled in the entire cohort.

PrEP Adherence

Among the 146 participants who had a POC urine test, 48 individuals (33%) had detectable levels of TFV, indicating a TFV concentration ≥1500 ng/mL; TFV levels were not detectable in 98 (67%) individuals (Table 2). When comparing PrEP adherence measured by the POC urine test to adherence measured by DBS, pill count, and self-report at the same visit, we found the strongest correlation with TFV-DP detectability in DBS. Overall, 117 individuals with the POC test also had results from TFV-DO at the same visit and 20 (17%) of these participants had detectable levels of TFV-DP. Among participants with detectable TFV-DP in DBS, 85% also showed TFV detection in POC TFV urine tests, while 19% without detectable TFV-DP had TFV in urine tests (kappa=0.51; 95% CI 0.34, 0.68). Using pill count, 40% of participants with high PrEP adherence had detectable TFV in POC urine tests, compared to 18% with low adherence (kappa=0.16; 95% CI 0.04, 0.29). Among those with high self-reported PrEP adherence, 45% had detectable TFV levels in urine, while 22% of those with low self-report had detectable levels of TFV in urine (kappa= 0.23, 95% CI 0.08, 0.39). Most participants (59%) believed their PrEP intake was sufficient for HIV protection; 43% of those who believed they took enough PrEP had detectable TFV levels, while 20% who didn't think they took enough PrEP had detectable TFV (kappa=0.25; 95% CI 0.10, 0.49).

Changes in self-reported adherence and sexual behavior reporting

Comparing self-reported adherence before and after the introduction of the POC urine test, participants more frequently reported low PrEP adherence during visits with a POC urine test compared to visits without the test (53% versus 27%, odds ratio [OR] 2.96, 95% confidence interval [CI]: 1.89, 4.67, p=0.001) (Table 3). The frequency of reporting condomless sex in the previous three months was more common during visits where there was POC urine testing compared to visits without the test (75% versus 68%, OR 1.47, 95% CI: 1.04, 2.06, p =0.03). There

was no significant difference in the frequency of reporting condomless sex in the previous week during visits with the POC test and visits without the POC urine test (OR 0.75, 95% CI 0.47, 1.19, p=0.2).

Overall, self-reported high PrEP adherence aligned with detectable TFV-DP in DBS at 57% of visits with both measures available (229 visits including 126 participants). When evaluating changes in the accuracy of self-reported PrEP adherence after the introduction of the POC urine test, we found that, during visits where the POC test was administered, there was a 61% concordance between self-reported PrEP adherence and adherence level measured by DBS. In contrast, concordance was 24% between self-reported PrEP adherence and adherence level measured by TFV-DP detectability in DBS during visits where a POC urine test was not conducted. Thus, the accuracy of self-reported adherence was statistically greater when the POC urine test was administered (OR 4.86, 95% CI: 2.85, 8.30, p<0.001) (Table 4).

Discussion

In this study, we evaluated the utility of using a urine POC assay to assess TFV adherence in the context of PrEP adherence monitoring and counseling of young Ugandan women using data from a prospective cohort. We observed that the introduction of a POC urine test for TFV substantially improved the accuracy of self-reported PrEP adherence. We also saw a moderate concordance between the POC urine TFV and TFV-DP in DBS and greater reports of condomless sex and low PrEP adherence when the POC urine test was used. Therefore, the POC urine test measuring TFV could play a vital role in facilitating more accurate reporting of these behaviors for HIV prevention and PrEP adherence counseling that aligns with actual behavior.

Scalable, low-cost interventions, such as POC TFV urine assays, are essential for supporting PrEP use among women in sub-Saharan Africa. However, drug-level testing is not

widely available due to cost and logistics. Therefore, there is a reliance on self-reported adherence to guide adherence counseling, especially in implementation studies and in clinical practice. However, findings from a variety of research and implementation programs underscore challenges with self-report (8,12,84). Two early PrEP efficacy clinical trials conducted among African women (VOICE and FEM-PrEP) failed to show the efficacy of oral PrEP against HIV acquisition, mainly due to poor adherence to the study medications, as measured by plasma TFV levels (8,12,85). However, in both studies, more than 90% of the study participants self-reported high adherence and had pill counts consistent with high adherence. Reasons for misreporting included fear of being terminated from the trial and anticipated negative reactions, including being scolded by staff, increased length of a clinic visit, and mistrust of the product or providers (84,86). In a subsequent qualitative study, VOICE participants suggested that having real-time adherence monitoring would facilitate honest reporting and adherence discussions (86). Our results show that the introduction of the POC urine TFV test may increase the accuracy of self-reported adherence. As such, the POC urine test could play a pivotal role in research and clinical settings by reducing misreporting and increasing the opportunity for early intervention with adherence counseling, especially when PrEP use levels are less than optimal.

We also found that participants were more likely to report engaging in condomless sex and having low PrEP adherence when the POC urine TFV test was used during their visit. More truthful self-reported behaviors could facilitate open discussions between providers and PrEP users about HIV risk and effective adherence to achieve prevention effectiveness. Furthermore, considering the intricate interplay of factors influencing oral PrEP adherence, having evidence of PrEP usage through the POC urine TFV test could enable providers to tailor their counseling messages to individual needs. In a recent study on the feasibility and acceptability of the POC urine test,

providers indicated that real-time adherence results empowered them to offer evidence-based counseling (87). Additionally, the POC urine test results could serve as a valuable tool for validation among PrEP users seeking confirmation of adherence (87). However, sensitivity is necessary when addressing negative results, ensuring that participants do not feel penalized for such outcomes (66). In our study, some participants were insistent on having good adherence even when the POC urine test indicated the absence of TFV. This indicates the importance of discussing the utility of POC urine tests as a supplementary means to address recall-related challenges of self-report rather than a means to verify the accuracy of clients' self-reported PrEP use. Using a client-centered approach, study counselors discussed the needs and challenges of the participants and were able to discuss strategies to improve adherence.

Further research is needed to evaluate the utility of POC urine TFV testing to monitor PrEP adherence and inform provider decision-making in clinic settings. However, our findings indicate that the POC urine TFV test could play an essential role in PrEP adherence counseling, particularly in a low-resource setting, since it is projected to be low-cost once available commercially. Additional research is needed to estimate the effectiveness of the test when integrated into a PrEP program and used consistently with participants or on a less frequent basis (e.g., a “spot check”).

Limitations

Our study has several limitations. The introduction of the point-of-care urine test occurred midway through the study, and as a result, many participants had already completed most of their follow-up visits. This led to fewer data points available for conducting a meaningful before-and-after comparison following the test's introduction. Additionally, we were unable to evaluate the long-term impact of the point-of-care urine TFV test on adherence over time. Furthermore, there might be misclassification due to the short recall period of the urine TFV test and an inability to rule out

"white coat dosing," whereby a single pill taken just before the POC urine test would result in a positive test and not reflect consistent use. Thus, individuals who had recently taken PrEP might have been wrongly classified as adherent. In contrast, those who were generally adherent but had missed doses in the days leading up to the test could be incorrectly classified as non-adherent.

Conclusions

Ours is one of the first studies to use the POC TFV test in a PrEP program among young women, showing the benefits of the assay. The introduction of the POC TFV urine test into a PrEP study yielded increases in the accuracy of self-reported information about PrEP adherence and sexual behavior. More accurate reporting of behavior can encourage honest and open dialog between providers and PrEP users and ultimately improve support for those using PrEP for HIV prevention.

Competing interests

All authors declare no competing interests.

Authors' contributions

Study conceptualization: KZ and RH. Data analysis: KZ. Writing – original draft: KZ and RH. Writing – review and editing: All authors. All authors participated in the critical review and have read and approved the final manuscript.

Acknowledgments

Our sincere gratitude goes to the women who participated in this study for generously giving their time, samples, and information to the study team. We are also grateful to the study team members and our collaborative partners in Uganda and the US who helped to make this study possible. The study was funded by the Eunice K. Shriver National Institute for Child Health and Human Development (R01HD089843) and FTC/TDF medication was donated by Gilead Sciences LLC. KZ was supported by the University of Washington STD/AIDS Research Training Grant (T32 AI07140).

Tables

Table 1: Demographic characteristics of participants who had point-of-care urine testing

Characteristic	N = 146 Median (IQR) or N (%)
Age (years)	19 (18, 21)
Relationship status	
Single	18 (12%)
Married/in steady partnership	128 (88%)
Years of education	10 (7, 11)
Participant earns income	
No	74 (51%)
Yes	72 (49%)
Travel time to research clinic	
<1 hour	24 (16%)
1-2 hours	116 (80%)
>2 hours	6 (4%)
Partner provides financial support	
No	5 (3%)
Yes	141 (97%)
Partners HIV status	
Negative	46 (32%)
Unknown	99 (68%)
Any condomless sex, last 3 months	
No	35 (24%)
Yes	111 (76%)
Any condomless sex, last week	
No	82 (56%)
Yes	64 (44%)
Multiple partners in past 3 months	
No	47 (32%)
Yes	99 (68%)
Contraception choice	
Condoms	48 (33%)
DMPA	98 (67%)

Table 2: POC urine test results and PrEP adherence by pill count and self-reported sexual behavior

	Urine POC test result			
Characteristic	**All Tested, N = 146 (column %)**	**Not detectable, N = 98 (row %)**	**Detectable, N = 48 (row %)**	**Kappa (95% CI)**
Adherence by pill count, past month				0.16 (0.04, 0.29)
Low	45 (31%)	37 (82%)	8 (18%)	
High	101 (69%)	61 (60%)	40 (40%)	
Adherence by DBS				0.51 (0.34, 0.68)
Undetectable	97 (83%)	79 (81%)	18 (19%)	
Detectable	20 (17%)	3 (15%)	17 (85%)	
Self-reported PrEP use, past month				0.23 (0.08, 0.39)
Low	77 (53%)	60 (78%)	17 (22%)	
High	69 (47%)	38 (55%)	31 (45%)	
Participants think she took PrEP well enough to be protected from HIV in past month				0.25 (0.10, 0.40)
No	59 (41%)	47 (80%)	12 (20%)	
Yes	84 (59%)	48 (57%)	36 (43%)	

Table 3: Self-reported adherence and sexual behavior change before and during the POC test

	Visit with point of care urine test			
	Yes	No	OR (95% CI)	p-value
Self-reported Adherence				
High	69 (47%)	106 (73%)	Ref.	
Low	77 (53%)	40 (27%)	2.96 (1.89, 4.67)	0.001
Any condomless sex, last 3 months				
Yes	110 (75%)	98 (68%)	1.47 (1.04, 2.06)	0.029
No	36 (25%)	47 (32%)	Ref.	
Any condomless sex, last week				
Yes	36 (25%)	44 (30%)	0.75 (0.47,1.19)	0.2
No	110 (75%)	101 (70%)	Ref.	

Table 4: The accuracy of self-reported past month PrEP at visit during which the POC urine test was administered compared to at the prior visit

	Before POC test	**POC test administered**	**OR (95% CI)**	**p-value**
Self-reported adherence matches DBS				
Yes	27 (24%)	71 (61%)	4.86 (2.85, 8.30)	<0.001
No	85 (76%)	46 (39%)	Reference	

Chapter 4: High preference for injectable pre-exposure prophylaxis among young women in Kenya

Title: High preference for injectable pre-exposure prophylaxis among young women in Kenya

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This work was funded by the National Institute of Mental Health of the US National Institutes of Health (grant # R01 MH123267). Kidist Zewdie was supported by NIH T32 AI07140. Dr. Heffron was supported by K24MH123371.The project funders had no role in study design or writing of the report.

Abstract

Background: Longer-acting HIV pre-exposure prophylaxis (PrEP) products are effective options for HIV prevention that require less user dependence. As programs are preparing to launch delivery of these longer-acting products, it is important to understand users' needs and preferences.

Setting: We conducted a cross-sectional study among women seeking services at 12 family planning clinics in Kisumu, Kenya.

Methods: Participants were sexually active HIV-negative women ≥15 years old, with at least one characteristic that is more common among women who acquire HIV. We assessed PrEP product preferences among PrEP-experienced and inexperienced women. We used descriptive statistics to summarize participants' characteristics, product preferences, and willingness to use different PrEP modalities. We used univariate and multivariate models to assess factors related to preferences for injectable PrEP.

Results: A total of 457 participants were enrolled, including 341 with no oral PrEP experience and 116 with recent oral PrEP experience. The median age was 26 [IQR:23-30], 83% were married or cohabiting and 31% reported using injectable contraceptives. Among participants without prior PrEP experience, 74% preferred injectable PrEP, 19% preferred oral PrEP, and 4% preferred the vaginal ring. Among previous oral PrEP users, 82% preferred injectable PrEP, 16% preferred oral PrEP, and only 2% preferred the dapivirine vaginal ring. Only perceived PrEP stigma was significantly associated with injectable PrEP preference (PR: 1.21, 95% CI 1.09, 1.37, P=0.001).

Conclusion: Reproductive-age women in Kenya have a strong interest in long-acting injectable PrEP. Product rollout and implementation need to consider women's preferences and devise best approaches to deliver injectable PrEP.

Keywords: Preference, HIV prevention, long-acting PrEP, Dapivirine vaginal ring, cabotegravir

Introduction

Daily oral pre-exposure is highly effective in reducing the risk of HIV among women with consistent daily adherence (6,11). However, the effectiveness of daily oral PrEP wanes in the face of low adherence and persistence, which are common barriers to its success among young African women (8,12,13). Since proven efficacious, programmatic data and evaluations have demonstrated that more than 50% of young African women discontinue PrEP in the first few months and <25% had the required adherence level for HIV prevention (8,12,66,68,76). Young women have cited reasons for PrEP discontinuation or low adherence that include side effects, pill burden, difficulty concealing pill-taking, negative consequences of inadvertent disclosure, and frequent visits to clinics (13,16–18). Thus, alternative PrEP products that require less frequent dosing, and offer greater discreetness are needed to address users' needs and preferences.

Currently, alternative PrEP products that are less user-dependent, including the monthly dapivirine vaginal ring (DVR) and 2-monthly injectable cabotegravir (CAB-LA), are safe and effective among African women and are in the process of being integrated into the HIV prevention toolkit. In two phase 3 randomized clinical trials, dapivirine vaginal ring reduced the risk of HIV acquisition in cisgender women by approximately 30% (22,88) and results from open-label extension studies as well as subgroup analysis from the two trials suggested a greater level of protection among women with consistent use of the ring (23,88–90). Based on these data, the dapivirine vaginal ring received a positive opinion from the European Medicines Agency (EMA) and the World Health Organization currently recommends the dapivirine vaginal ring as an additional prevention option for women at substantial risk of HIV (26,91). Multiple trials have shown that Cabotegravir is safe and well-tolerated as HIV treatment as well as prevention (20,92–94). In addition to being approved by the U.S. Food and Drug Administration (FDA) in December

2021, injectable CAB has also received approval in several other countries, including Australia, Zimbabwe, and Malawi, and has been submitted to regulatory authorities for approval in many others (95,96).

Apart from addressing PrEP adherence challenges, increasing the variety of PrEP products including longer-acting injectable and vaginal rings increases options and should theoretically increase overall use of HIV prevention products. Previous studies on family planning methods have shown that increasing product choice increases the number of women utilizing contraceptives (69,70). Therefore, as programs are preparing to launch delivery of these longer-acting products, it is important to understand users' needs and preferences. In this study, we aim to evaluate preferences and willingness to use novel PrEP products (i.e., injectable cabotegravir and dapivirine vaginal ring) among oral PrEP-experienced and inexperienced women in Kenya when they were accessing family planning services.

Methods

Study design and subjects

Our study is nested within the research cohort of a parent study, the Family Planning plus HIV prevention Project (FP-Plus). The FP-Plus is a prospective, open-label implementation science project to catalyze the integration of comprehensive HIV prevention and PrEP care services for adolescent girls and young women accessing family planning in 12 clinics in Kisumu, Kenya (ClinicalTrials.gov #NCT04666792). The project includes a nested prospective open cohort which enrolled sexually active HIV-negative women, with at least one characteristic that is more common among women who acquire HIV (e.g. inconsistent or condom use; engaging in transactional sex; recent bacterial sexually transmitted infection, etc.), initiating oral PrEP, and ≥15 years. Women enrolled in the research cohort had visits at enrollment, one month and then

quarterly for up to 24 months with HIV testing, and a brief questionnaire on demographics, mental health, sexual behaviors, HIV and STI risk, family planning, and HIV prevention methods used.

Partway through the FP-Plus study, we were approved to include an ancillary component to measure preferences and willingness to use different PrEP modalities. Since the study was already underway, we administered an 8-item questionnaire assessing preferences and willingness to use different PrEP modalities to both newly enrolling women and those who had completed their 12-month visit. The resulting cross-sectional cohort included women newly enrolling in the study and women who were followed for a year. All questionnaires were translated into local languages and verified by performing an independent back-translation. The PrEP preferences questionnaire was administered from June 2021 to January 2023. After providing a brief description of the 2-monthly injectable cabotegravir (CAB-LA) and monthly dapivirine vaginal ring, we assessed product awareness, preferences of PrEP products; reasons for preferences; concerns about the products and preferred settings for accessing the products. To measure awareness and interest in each product, we asked participants two separate questions: "Have you heard of injectable PrEP/vaginal ring before today?" and "Would you consider using injectable PrEP/vaginal ring to protect yourself against HIV?" To understand perceived concerns about the products, we asked participants to indicate their concerns from a list of common concerns or use free text to describe them. To measure the participant's willingness to switch to newer products, we asked: "If you were using oral PrEP and the injection/vaginal ring became available to you, would you want to switch to the injectable/vaginal ring?" We then assessed product preference "Which type of PrEP methods would you prefer if they were to be offered?" Response options included: 1) Injectable PrEP, 2) Vaginal ring, 3) Oral PrEP, 4) Other methods.

Statistical analysis

We used descriptive statistics to summarize participants' characteristics, product preferences, and willingness to use different PrEP modalities. We used univariate models to assess factors related to preferences for each product as well as a willingness to use each type of PrEP product. We used generalized linear models with binomial parametrization and log link to estimate prevalence ratios. We used a multivariate model to evaluate if any demographic, behavioral, and clinical characteristics are independently associated with a longer-acting injectable PrEP. All analyses were conducted using R version 4.2.2.

Ethical considerations

University of Washington Human Subjects Division and the Kenyatta National Hospital-University of Nairobi Ethical Review Committee reviewed and approved the study protocol, informed consent forms, data collection tools, and patient education materials. We obtained written informed consent from study participants before conducting any procedures.

Results

Participant characteristics

Overall, 457 (72%) participants completed the questionnaire. At enrollment, we administered the questionnaire to 341 participants who did not have any prior exposure to oral PrEP. We also administered the questionnaire to 116 participants during their year one follow-up visit and thus, they had been using oral PrEP for a year [Table 1]. Overall, the median age was 26 years [interquartile range (IQR):23-30], 55% had completed at least high school level education and

83% were married or cohabiting. In terms of contraceptive methods, 31% reported using injectables, 23% were using implants, and 18% were using oral contraceptives. While 9% had more than one sexual partner, 78% did not know their partner's HIV status and 11% reported condom use in recent vaginal sex. Additionally, 23% believed their sexual behavior exposes them to HIV. The demographic characteristics of PrEP experienced and inexperienced participants were similar at baseline.

Willingness and preference for new PrEP products

Among 341 participants who had not used PrEP previously, 7% reported having heard of dapivirine vaginal ring, 16% expressed willingness to use dapivirine vaginal ring and 10% indicated they would choose dapivirine vaginal ring instead of oral PrEP if the ring were to be available to them [Figure 1]. Among oral PrEP experienced users (N=116), 14% reported having heard of dapivirine vaginal ring, 8% expressed willingness to use it, and 6% indicated they would switch from oral PrEP to dapivirine vaginal ring. In contrast to dapivirine vaginal ring, a higher percentage of PrEP-inexperienced participants were familiar with injectable PrEP (CAB-LA). Out of the participants with no oral PrEP experience, 13% had heard about injectable PrEP, 81% expressed willingness to use injectable PrEP, and 77% indicated they would choose injectable PrEP instead of oral PrEP if it were to be available to them. Among participants who had previous experience with oral PrEP, 38% had heard about injectable PrEP, 91% expressed a willingness to use injectable PrEP, and 92% indicated they would like to switch from oral PrEP to injectable PrEP.

Participants concerns about the dapivirine vaginal ring and injectable PrEP

Among participants who have not used PrEP previously, 48% reported concerns about pain caused by wearing the ring, while 36% were worried about experiencing pain during ring insertion [Figure 2]. Additionally, 42% of the participants expressed concern about having an object inside their vagina. Other concerns included worrying about their partner feeling the ring (28%) and the possibility of the ring being expelled (24%). Notably, the effectiveness of the ring (9%) and cost (6%) were not the most frequently reported concerns. Similarly, among PrEP-experienced users, the characteristics of the rings were identified as major concerns. PrEP-experienced users expressed concerns about having an object inside their vagina (55%), experiencing pain from wearing the ring (54%), their partner feeling the ring (49%), and the possibility of the ring being expelled (45%).

Among participants with no experience with PrEP, frequently reported concerns about injectable PrEP include not having enough information about the product (41%), concerns about potential side effects (40%), pain from the injection (29%), having to return for injection (14%), and fear of needles (12%). Similarly, experienced PrEP users reported that not having enough information about the product (57%) was their primary concern regarding injectable PrEP [Figure 3]. They also expressed concerns about potential side effects (35%), pain from the injection (16%), and fear of needles (6%).

PrEP Product Preference

Among participants without prior experience using PrEP, 74% preferred injectable PrEP, 19% preferred oral PrEP, and only 4% expressed a preference for the vaginal ring. Similarly, among PrEP-experienced users, 82% preferred injectable PrEP, while 16% preferred oral PrEP, and the dapivirine vaginal ring was preferred by only 2% of the participants. Factors associated with preference for injectable PrEP include prior experience with PrEP (PR: 1.11, 95% CI: 0.99, 1.23,

p=0.05) and perceived PrEP stigma (PR: 1.21, 95% CI 1.09, 1.37, P=0.001) [Table 2]. Age, marital status, education, use of injectables for family planning, number of sexual partners, HIV status of the sexual partner, condom use, and HIV risk perception were not associated with preference for injectable PrEP over other PrEP types. We did not find any significant associations between these variables and preference in the multivariable model.

Discussion

Our study aimed to evaluate preferences for and willingness to use newer PrEP products among participants who had previous experience using oral PrEP and those who did not. We found that an overwhelming number of users were willing to use injectable PrEP and would like to switch from their current PrEP regimen to injectable PrEP if it were available to them. Our findings suggest that in this population of reproductive-age women in Kenya, adding injectable PrEP to the HIV prevention toolkit could potentially increase PrEP use and overall coverage of HIV prevention.

A previous study conducted among South African adolescent women (UChoose) found a preference for injectable HIV prevention options, followed by a vaginal ring and lastly oral PrEP (97). In our study, we also found that injectable PrEP was most preferred, followed by oral PrEP. In a study conducted among Black women in the U.S., oral PrEP was most preferred, followed by injectable and vaginal ring (98) indicating that product preference likely varies by geography, familiarity with a product, and other social and structural factors that influence product choices (17,21,99). It is essential to consider these variations when developing an implementation plan to include these novel methods in HIV prevention tool kits. Furthermore, it is important to

acknowledge that no single HIV prevention method appeals to everyone nor is likely to align with a person's prevention needs throughout their sexually active life span. Increasing the types of products available for HIV prevention is likely to increase the number of people protected against HIV (69,70). Thus, providing a choice of different PrEP products is crucial in ensuring that women have prevention options based on their individual needs and interests.

Intimate or romantic male partners often influence heterosexual cisgender women's HIV prevention choices –some could potentially be supportive and others could have a negative reaction to PrEP use (100–102). Negative reactions to PrEP use by sexual partners have included confiscating PrEP pills, physical violence, and demanding discontinuation (59,102). Similar to what is reported by the ASPIRE study (102), we found that fear of partners feeling or discovering the ring during sexual activity was a major concern among our study participants. While both dapivirine ring and injectable CAB could offer discreet HIV prevention options for women, male partner support is associated with better product adherence(103). Thus, strategies that aimed to increase male partner involvement and mitigate negative reactions could increase product preference and use.

Women who perceived high PrEP stigma in their community were also more likely to choose longer-acting injectable PrEP. Perceived or experienced PrEP stigma is a significant barrier to PrEP use (104–107) and consequences of this stigma have included incorrect assumptions that oral PrEP is actually HIV treatment and that the use of oral PrEP implies engagement with numerous sexual partners (105–109,109). The preference for longer-acting injectable PrEP highlights the importance of addressing stigma as a barrier to PrEP use. Providing more discreet options, such as longer-acting injectable PrEP, can help reduce stigma and increase access to PrEP. However, it is important to note that injectable PrEP might need to

be administered in medical settings, including HIV clinics, and the stigma associated with attending regular clinic visits and being at an HIV clinic might still hinder PrEP users from choosing this prevention option. Making new PrEP products available in non-HIV clinic settings, such as family planning clinics, is also a priority for implementation.

Unlike oral PrEP, which requires daily pill-taking, CAB-LA, and the dapivirine vaginal ring do not require daily adherence and can be a prevention option for women that struggle with forgetfulness and daily pill-taking. The use of long-acting contraceptives by the majority of study participants suggests that longer-acting PrEP options, like injectable CAB and the dapivirine vaginal ring, could be preferred by a significant number of women. We saw a trend towards a greater preference for longer-acting PrEP in women who experienced using long-acting contraceptives. However, we did not observe a significant correlation between the preference for injectable PrEP and the use of injectable contraceptives indicating that preference for longer-acting PrEP may not be solely driven by previous experience with long-acting contraceptives. Further research is needed to better understand the factors influencing women's preferences for different PrEP products in this population.

In our study, preference for the ring was low compared to oral and injectable PrEP. Participants noted product attributes as the reason for their concern regarding the ring. However, participant preference for the ring might change if users have the option to experience using the ring. In a study conducted among young women in sub-Saharan Africa (REACH), participants who had experience with both oral PrEP and the ring opted for using the ring after experiencing both (110), indicating that familiarity with the product is an important consideration when choosing products (102). Additionally, women have reported not having adequate information about injectable PrEP. Therefore, the implementation of these products must include

comprehensive information about each product, along with a possible demonstration of how to properly use them.

Our study investigated hypothetical preferences, and participants were not required to use the products during the visit nor were the novel products available to show participants. Hence, the actual product preference might differ when individuals have a real choice in front of them. Future studies need to be conducted to assess the actual uptake of products and qualitatively explore the reasons behind product preferences. It is worth noting that in many African settings, injectable contraceptives are commonly used, and the implementation of injectable PrEP requires careful consideration of the best approach for co-delivery with injectable contraceptives. In addition, programs would need to prioritize working with communities to develop effective strategies for the introduction of these new products and strengthen health systems to better deliver and integrate these new prevention options. Collaborative efforts with governments and funding agencies are also necessary to ensure equitable access to these products and to eliminate cost barriers that may hinder women in low- and middle-income countries from accessing them.

Competing Interests

All other authors declare no competing interests.

Authors' contributions

Study conceptualization and funding acquisition: KKM, Data collection tool development: KKM, JK, CG, and DM; Data collection: KKM, JK, DM, CW, VK, IC, TO, MB, EA, SO, BO, DS, CG, JM; Project administration: KKM, JK, DM, JM. Data analysis: KZ. Writing – original draft: KZ, RH, and KKM. Writing – review and editing: All authors. All authors participated in the critical review and have read and approved the final manuscript.

Acknowledgment

We thank the women who participated in this project and the staff at implementing facilities and the project staff for their motivation and dedication.

Funding

This work was funded by the National Institute of Mental Health of the US National Institutes of Health (grant #R01 MH123267). Kidist Zewdie was supported by NIH T32 AI07140. Dr. Heffron was supported by K24MH123371.The project funders had no role in study design or writing of the report.

Tables and Figures

Table 1: Participant characteristics

Characteristic	Overall, N = 457 (N (%) or median (IQR))	Oral PrEP inexperienced, N = 341 (N (%) or median (IQR))	Oral PrEP experienced, N = 116 (N (%) or median (IQR))
Age (years)	26 (23, 30)	26 (22, 30)	28 (24, 32)
Education			
< High school	207 (45%)	141 (41%)	66 (57%)
≥High school	250 (55%)	200 (59%)	50 (43%)
Marital status			
Married/Cohabiting	379 (83%)	272 (80%)	107 (92%)
Separated/divorced/Widowed	78 (17%)	69 (20%)	9 (7.8%)
Earns her own income	208 (52%)	179 (53%)	29 (48%)
Currently breastfeeding	187 (47%)	165 (49%)	22 (37%)
Family planning method			
None	55 (12%)	50 (15%)	5 (4%)
Injectable	140 (31%)	92 (27%)	48 (41%)
IUCD	15 (3%)	11 (3%)	4 (3%)
Implant	107 (23%)	79 (23%)	28 (24%)
OCP	83 (18%)	58 (17%)	25 (22%)
Condoms	50 (11%)	45 (13%)	5 (4%)
Other	9 (2%)	7 (2%)	2 (2%)
Partner's education			
< High school	113 (26%)	73 (22%)	40 (35%)
≥High school	325 (74%)	252 (78%)	73 (65%)
Partner provides financial support	359 (91%)	265 (92%)	94 (89%)
Number of Sexual partners in the past 3 months			
0-1	415 (91%)	304 (89%)	111 (96%)
>1partner	42 (9%)	37 (11%)	5 (4%)
HIV status of the last sexual partner			
HIV negative	84 (19%)	68 (20%)	16 (14%)
HIV positive	16 (4%)	10 (3%)	6 (5%)
Unknown	353 (78%)	262 (77%)	91 (81%)
Condom was used at most recent vaginal sex	50 (11%)	40 (12%)	10 (9%)
High HIV risk perception	103 (23%)	86 (25%)	17 (15%)

PrEP Status at enrollment			
Initiated PrEP	303 (67%)	196 (57%)	
Declined PrEP	149 (33%)	145 (43%)	
Perceived PrEP Stigma	293 (64%)	200 (59%)	93 (80%)

Table 2: Predictors of injectable PrEP preference

	Injectable preference		Preference for injectable PrEP over other options			
Characteristic	**No, n = 111**	**Yes, n = 345**	**PR (95% CI)**	**P value**	**Adjusted PR (95% CI)**	**P value**
Age (years)						
<25	47 (27%)	125 (73%)	Ref.		Ref.	
>=25	64 (23%)	220 (77%)	1.07 (0.96, 1.20)	0.3	1.02 (0.75, 1.33)	0.9
Education						
< High school	42 (20%)	165 (80%)	Ref.		Ref.	
≥High school	69 (28%)	180 (72%)	0.91 (0.82, 1.01)	0.06	0.97 (0.75, 1.26)	0.8
Marital status						
Separated/divorced/Widowed	23 (28%)	58 (72%)	Ref.		Ref.	
Married/Cohabiting	88 (23%)	287 (77%)	1.07 (0.93, 1.26	0.4	1.06 (0.77, 1.51)	0.7
Earns her own income						
No	48 (25%)	143 (75%)	Ref.		Ref.	
Yes	52 (25%)	156 (75%)	1.00 (0.89, 1.12)	0.9	0.99 (0.77, 1.27)	0.9
Family planning method						
Other methods	84 (27%)	231 (73%)	Ref.		Ref.	
Injectable	27 (19%)	114 (81%)	1.10 (0.99, 1.22)	0.07	1.01 (0.78, 1.31)	0.9
Partner's education						
< High school	20 (18%)	92 (82%)	Ref.		Ref.	
≥High school	87 (27%)	238 (73%)	0.89 (0.80, 1.01)	0.04	0.93 (0.69, 1.26)	0.6
Number of sexual partners in the past 3 months						
0-1	103 (25%)	305 (75%)	Ref.		Ref.	
>1partner	8 (17%)	40 (83%)	1.11 (0.94, 1.26)	0.12	1.03 (0.68, 1.51)	0.9
HIV status of the last sexual partner						
HIV negative	33 (30%)	76 (70%)	Ref.		Ref.	
HIV positive	2 (11%)	16 (89%)	1.27 (0.72, 2.13)	0.4	1.26 (0.64, 2.28)	0.5
Unknown	75 (23%)	253 (77%)	1.11 (0.86, 1.44)	0.4	1.08 (0.81, 1.46)	0.6
Condom used at most recent vaginal sex						
No	99 (25%)	304 (75%)	Ref.			

Yes	11 (21%)	41 (79%)	1.05 (0.88, 1.19)	0.6	1.04 (0.70, 1.50)	0.9
Risk perception						
Low	92 (26%)	265 (74%)	Ref.		Ref.	
High	19 (19%)	80 (81%)	1.09 (0.96, 1.21)	0.14	1.10 (0.82,1.47)	0.5
Perceived PrEP stigma						
Low	60 (33%)	122 (67%)	Ref.		Ref.	
High	51 (19%)	223 (81%)	1.21 (1.09, 1.37)	0.01	1.19 (0.93, 1.53)	0.2
Oral PrEP experienced						
No	90 (26%)	250 (74%)	Ref.		Ref.	
Yes	21 (18%)	95 (82%)	1.11 (0.99, 1.23)	0.05	1.14 (0.82, 1.55)	0.4

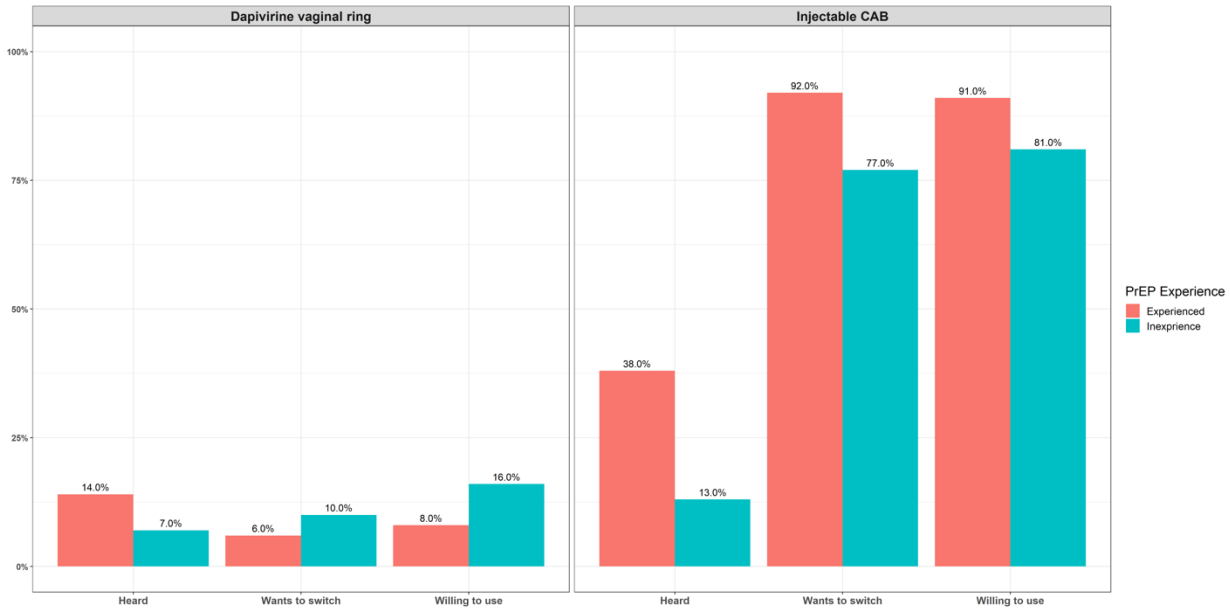

Figure 1: Willingness and preference to use new PrEP products.

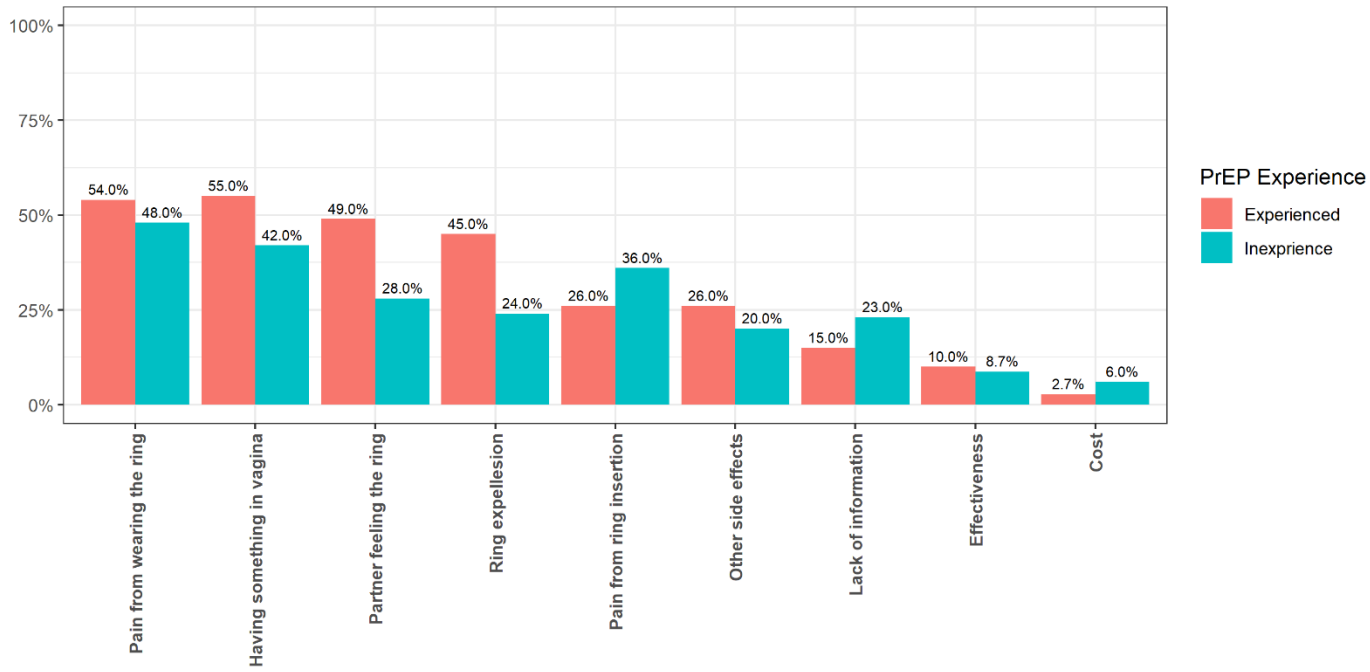

Figure 2: Participant concerns about dapivirine vaginal ring as HIV PrEP

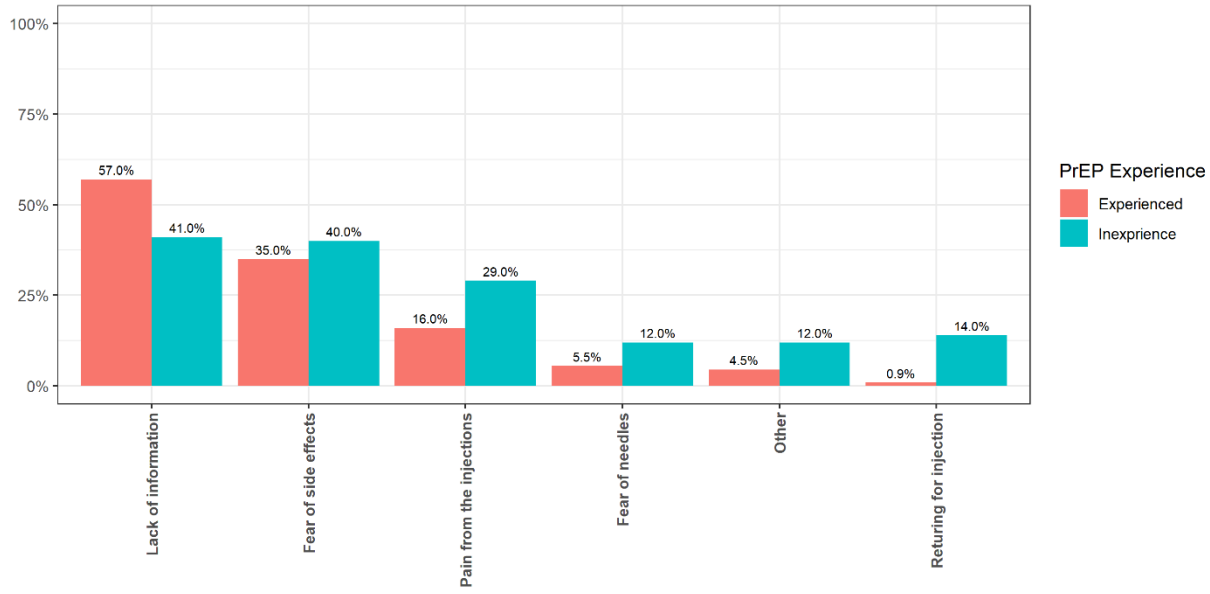

Figure 3: Participant concerns about injectable cabotegravir as HIV PrEP

Chapter 5: Discussion

This dissertation contributes to efforts to optimize the delivery of daily oral PrEP and novel PrEP products to young women in sub-Saharan Africa. By leveraging data from prospective cohorts, we report on the combined effect of TDF-based oral PrEP and pregnancy on maternal bone density and provide novel data on the use of point-of-care urine TFV testing to support oral PrEP adherence counseling for young African women. We also apply data from a cross-sectional cohort of young women accessing family planning to examine the preferences of young women for longer-acting PrEP products that are up-and-coming. The findings from these studies inform strategies to support PrEP adherence and persistence among women during pregnancy and the postpartum period, provide novel data on the use of POC TFV testing to support counseling on daily oral PrEP adherence, and inform decisions on the delivery of novel PrEP products to young African women.

The safety of TDF-based oral PrEP on bone health during pregnancy

In Chapter 2, we explore the joint effect of TDF-based PrEP and pregnancy on bone mineral density among young African women. We observe declines between 2.5% and 3.0% in BMD among pregnant women using PrEP. This is consistent with what we expect to see in BMD reduction among pregnant women; generally, BMD decreases between 2-3% during pregnancy at different anatomical points (111). Furthermore, our additional analysis aims to differentiate the impact of PrEP on BMD from that of pregnancy, indicating that the BMD loss is primarily attributed to pregnancy rather than TDF-based PrEP. It is important to note that the level of exposure to PrEP in our study population may have impacted our ability to observe the effect of consistent TDF exposure on bone health during pregnancy. Additionally, due to our small sample size, we are not able to make a conclusive statement on the effect of TDF-based oral PrEP on the bone mineral density of pregnant women.

Studies of bone health during pregnancy and lactation after exposure to TDF-based PrEP are limited. However, studies on TDF exposure in lactating women living with HIV indicated that TDF-based ART exacerbates bone loss during lactation (112,113). These studies found a 2-3% decrease in BMD in postpartum women using TDF-ART compared to lactating women not using ART or who were not living with HIV indicating that TDF-based ART or PrEP exacerbates bone loss during pregnancy and breastfeeding (113,114). However, the clinical implications of these reductions – whether this reduction is related to osteoporosis and fragility fractures – have not yet been evaluated. In another study on the same cohort, we observe that women using DMPA and TDF-based HIV PrEP concurrently experience significant bone loss. A young woman who chooses to use TDF-based PrEP and DMPA concurrently for multiple years before the start of pregnancy may start with already lower BMD, which might further be exacerbated by pregnancy and breastfeeding. As such, questions regarding prolonged exposure to TDF-based PrEP and DMPA, particularly at an early age where bone mineral density is yet to reach a peak, are worth investigating. In addition, future studies are needed to evaluate the use of vitamin D and calcium supplementation during pregnancy and breastfeeding to counteract the effect of TDF-PrEP.

Making the case for increasing the choice of products for pregnant and lactating people

Currently, TDF-based oral PrEP is the only approved product for use during pregnancy. However, our results from Chapter 2 highlight the pressing need for a choice of products for pregnant and postpartum women that do not affect their bone mineral density, are safe for both the mother and the fetus, and are effective at preventing HIV acquisition during pregnancy. This is particularly important for young African women given the robust cycle of fertility and high rate of breastfeeding, yielding a large proportion of their time pregnant or postpartum in many

settings. A variety of PrEP products are currently in development, including short-acting, long-acting, and multipurpose prevention options and the list of approved products is expanding. Currently, four products are approved for use as PrEP: oral PrEP with tenofovir disoproxil and emtricitabine (TDF/FTC), oral PrEP with tenofovir alafenamide and emtricitabine (F/TAF), the dapivirine vaginal ring, and injectable cabotegravir (115). However, data on the safety of these products for pregnant and breastfeeding women are minimal and limited to TDF/FTC and the dapivirine ring.

A combination of Tenofovir alafenamide (TAF) and emtricitabine (F/TAF), brand name Descovy, has been approved for use in MSM and transgender women since 2019 (116). Data on cisgender women is not yet available but a clinical trial is underway that evaluates the efficacy of both long-acting injectable lenacapavir and daily oral F/TAF among African women aged 16 to 25 years relative to F/TDF (117). If data from the trial show F/TAF to be efficacious, daily F/TAF could be an alternative oral PrEP product for women with a better safety profile on bone and renal health (118). Similar to TDF, TAF hydrolyzes to TFV in plasma, but at a significantly slower rate. As a result, plasma TFV levels in individuals using TAF are more than 90% lower in TAF users compared to those using TDF (119). The lower plasma TFV levels in plasma result in lower exposure of kidney and bone to the medication which might improve bone and renal safety outcomes for TAF users (119,120). Data on the pharmacokinetics and safety of TAF during pregnancy and postpartum are limited, and there are planned studies evaluating maternal and infant outcomes among women using a TAF-containing ARV regimen. For TAF to be available for pregnant women, the planned F/TAF trial for African women needs to demonstrate the efficacy of TAF in preventing HIV. Additionally, the safety data accumulating from the use of TAF in women for HIV treatment and along with any future open-label extension trials including

HIV-negative pregnant women need to show TAF to be safe for use during pregnancy. This means that it may take years before TAF becomes available for use by pregnant and postpartum women.

Injectable Cabotegravir (CAB) is currently approaching implementation, and although studies on its effect on bone mineral density are scarce, CAB has not been linked with bone mineral density loss; however, more studies are needed to reaffirm its safety (123). In addition, pregnant and breastfeeding women were excluded from CAB efficacy trials, and those who became pregnant during the trial discontinued CAB use as soon as pregnancy was detected (124). CAB is not yet approved for use during pregnancy, and an open-label extension study that includes pregnant and breastfeeding women is underway. In this extension, women are given the option to continue on CAB or switch to oral PrEP (TDF/FTC) when pregnant (125). Although the number of births to CAB-exposed mothers has been small to date, the available evidence suggests that the risk of adverse events during pregnancy is similar to other antiretrovirals, and there have not been any reported birth defects (126). Data from dolutegravir, an integrase inhibitor with similar characteristics to CAB, might help assess CABs safety during pregnancy (127). A study from Botswana using surveillance data reported a possible link between dolutegravir and neural tube defects, which led to a safety signal on dolutegravir (128,129). However, subsequent evidence showed that the risk of neural tube defects associated with dolutegravir was lower than what was first reported, and the WHO has since updated the recommendation to include pregnant women and women with childbearing potential (130–132). We are now several years beyond the initial approval of CAB as PrEP for women. Due to delays in CAB implementation, it may take time to have data from real-world implementation.

However, data from the open-label extension study could provide evidence for regulatory approval for pregnant women.

The Dapivirine vaginal ring is another longer-acting HIV prevention product that has been recommended by the WHO for at-risk women. With this product, Dapivirine is slowly released into vaginal tissue with low absorption elsewhere in the body, which might mean low side effects including on women's bone density; however, there is minimal available data. Data on the safety of the ring during pregnancy and breastfeeding are limited but reassuring (10–12). A recent study, MTN-042, showed that adverse events and pregnancy complications are uncommon in women using the dapivirine ring (134,135). Another study, MTN-043 showed that DVR poses no safety risk for infants from breastfeeding(136). Taken together, the results from these studies could warrant updates to the WHO guidelines to include DVR as an HIV prevention option for pregnant and breastfeeding women.

As highlighted by these discussions, for so long, pregnant, and lactating women have been excluded from clinical trials, including most large trials of PrEP. As such, for new HIV prevention and treatment products, the safety data during pregnancy and lactation come from post-market surveillance studies several years later. Studies on other ARV drugs indicate that the median time between the approval of ARV drugs and the availability of pharmacokinetic and safety data during pregnancy exceeds six years, creating an evidence gap for new HIV prevention products (137–139). Key evidence gaps include the absence of pregnancy-specific dosing, insufficient data on fetal safety, and a lack of data on maternal outcomes. Without the safety evidence, pregnant and lactating people are left without needed medical protection at times when their susceptibility to infection is elevated. In recent years, there has been a growing conversation on protecting pregnant and lactating people through research rather than from

research and on equitable inclusion in HIV prevention research (140,141). The Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) Project aims to promote the responsible inclusion of pregnant individuals in HIV research (141). The project put forth 12 specific actionable recommendations for the ethical inclusion of pregnant women in research (141). It is imperative to continue this discussion and to accelerate the equitable inclusion of pregnant and lactating people in HIV prevention research. It is also a reproductive justice issue where black and brown pregnant women with high risk for HIV and pregnancy complications are left unprotected.

New tools and product choices to increase PrEP utilization in young women

Pre-exposure prophylaxis (PrEP) with oral tenofovir (TDF) or TDF co-formulated with emtricitabine (TDF/FTC) is highly effective in reducing the risk of HIV infection among women with consistent daily adherence (6,11). However, PrEP adherence and persistence have been low among young African women (8,12,13). Oral PrEP implementation studies have shown that more than 50% discontinue PrEP in the first few months and <25% adhere to PrEP (8,12,68,76). Side effects, pill burden, difficulty concealing pill-taking, negative consequences of inadvertent disclosure, and frequent visits to clinics are some of the reasons cited by young women for PrEP discontinuation or low adherence (13,16–18). While young African women may struggle with oral PrEP persistence and adherence, this does not necessarily indicate a lack of interest in using PrEP for HIV prevention. Rather, it underscores the need for products that are more suited to their needs. In Chapter 4, we evaluated young women's preference for types of PrEP products and found that, in our study, young women overwhelmingly favored injectable PrEP products. This preference persisted regardless of their experience with oral PrEP, indicating a consistent preference for

longer-acting injectable PrEP products. In addition to the longer-acting formulation, injectable PrEP products might have been highly favored because of the familiarity of injectable contraceptives as they are widely used by women in sub-Saharan Africa.

Providing young women with a variety of PrEP options in type and methods of delivery that best suit their circumstances and HIV prevention needs will increase PrEP coverage and its public health impact. Previous studies on family planning methods have demonstrated that expanding the range of available options increases the uptake of contraceptives, persistence on the chosen method, and improves health outcomes (29). For young women who struggle with daily oral PrEP, longer-acting PrEP products such as injectables, rings, and implants eliminate the need for daily pill taking making it easier to sustain protection for a longer time without further action from the user. Regardless of the delivery method, scaling up PrEP access to young African women requires engaging young women with PrEP services. Integrating PrEP delivery into existing services such as family planning could make PrEP accessible to young women. For example, if injectable PrEP is administered at family planning clinics, women could align family planning visits with PrEP injection visits, reducing the frequency of time taken away from work or the need for regular travel. Synchronizing PrEP injections with contraceptive visits could also provide women with a method to conceal PrEP use, thereby avoiding inadvertent disclosure and associated stigma (32). As PrEP product choices are expanding, it is crucial to understand that users may want to switch from one product to another or stop and start using a product depending on their needs at a given time. Implementation studies would be needed to assess when and why users switch from one product to another. Taking lessons learned from family planning and contraception, PrEP implementation programs need to prepare to support young women in their method of choice at a given season in their lives.

In addition to the provision of a range of products, providing the necessary support using new tools and approaches to facilitate PrEP persistence for those at risk of HIV acquisition is also equally important. In Chapter 3, we explored the utility of drug level feedback using a point-of-care urine test measuring PrEP adherence in adherence monitoring and PrEP use counseling. Our results show that providing point-of-care urine tests to measure PrEP adherence facilitated more honest reporting of sexual and PrEP use behaviors, likely mediated by greater open dialogue between providers and PrEP users, and this enabled targeted counseling and adherence support for those facing challenges with PrEP use. The feasibility and acceptability of the novel POC test on long-term adherence among women using PrEP are not yet known, however, studies are underway (73). Clients have previously reported a mixed view on the utility of POC testing, where some clients are concerned about privacy, confidentiality, and autonomy of their care, and for others, the test provides reassurance regarding their HIV prevention (142). Given the interplay of different factors that affect PrEP adherence, it is important to develop appropriate counseling messages for individuals utilizing the POC test to monitor their adherence. The goal of adherence counseling would be to engage users in a discussion about their experiences with using PrEP in a non-judgmental manner, focusing on what the results mean to users regarding their HIV prevention goal rather than monitoring users' adherence (67). Further evaluation is needed to assess whether the point-of-care tests improve adherence over time and if the point-of-care test could be available outside of the clinic setting for young women to monitor their adherence outside of the medical setting. In addition, studies are needed to determine appropriate drug level cut-offs for pregnant women since pregnant women generally have a lower quantifiable drug level. As newer PrEP products become available, POC tests would need to be adapted to test their metabolites.

Preparing for a choice of PrEP product in a new era of HIV prevention

By the end of 2023, nearly 6 million people worldwide have started using oral PrEP, but the uptake still falls short of the UNAIDS target of reaching 10 million people at substantial risk of HIV by 2025 (44,45). Encouragingly, in 2024, there will be a range of PrEP options available to users for the first time since the introduction of oral PrEP in 2012. However, expanding access to these options for young African women requires positioning them at the center of both research and access to these products. Additionally, making pregnant and adolescent girls, as well as young women, a priority population for these prevention methods and committing to making these methods available, accessible, and affordable is crucial. Lessons learned from oral PrEP implementation and providing a choice of contraception could be used to inform the implementation of a range of PrEP products for young women (143). Studies have shown that for young women where HIV prevention is not a top priority in their lives, PrEP reach could be increased by positioning HIV prevention in their social and interpersonal contexts, and PrEP use can support them to better manage their relationships and contribute to reaching personal goals (144). In addition, framing PrEP in a broad context of HIV prevention needs for everyone instead of labeling the product for those at risk will reduce the stigma associated with using these products and increase their appeal to young women.

Because of systematic inequalities and gender discrimination, young women are particularly vulnerable to HIV and the UNAIDS 2025 roadmap to ending AIDS by 2030 includes combination prevention for adolescent girls and young women in high-prevalence locations as one of its pillars (145). In addition to increasing PrEP choices, reducing young women's vulnerability to HIV requires a comprehensive approach that is designed to address harmful

gender norms; end gender-based discrimination, inequalities, and gender-based violence; improve social protection; and support economic empowerment (146). Increasing access to quality education for adolescent girls will increase knowledge about HIV prevention tools. Improving gender equality ensuring young women are protected from gender-based violence, increased participation in decision-making about their reproductive and sexual health will reduce women's vulnerability to HIV (146).

Conclusion

In this dissertation, we deliver evidence that could inform strategies to support PrEP use during pregnancy and the postpartum period, provide novel data on the use of point-of-care TFV testing to support adherence counseling, and data to inform decisions on the delivery of novel PrEP products to young African women. This work highlights the importance of further assessments of the effect of quantifiable TDF-based PrEP use during pregnancy on maternal bone health, underscores the need for advancing research on alternative PrEP products that may have a lesser effect on bone health and could improve PrEP use during pregnancy. We also highlighted the importance of continuous research to advance novel tools used to optimize counseling and adherence support.

Our finding from Chapter 3 showed that young African women prefer longer-acting PrEP products, by understanding the preferences of PrEP users, our research informs future implementations of long-acting products when they become available for clinical use and will be useful for normative bodies considering user values and preferences in guideline development. As newer PrEP products are nearing large-scale implementation, there is a need for financial investments, making pregnant and adolescent girls, as well as young women, a priority

population for these prevention methods, and committing to making these methods available, accessible, and affordable.

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