HIV-1 Risk and Prevention Strategies for Women during Pregnancy and Postpartum

Kerry A. Thomson

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Reading Committee:

Renee Heffron, Chair

Jared Baeten

Grace John-Stewart

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Abstract

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Kerry A. Thomson

Chair of the Supervisory Committee:

Renee Heffron
Assistant Professor
Departments of Global Health and Epidemiology

HIV-1 is the leading cause of death worldwide among women of reproductive age, and this group is a priority to reach with effective HIV-1 prevention. There is great potential to provide HIV-1 interventions to women during the periconception, pregnancy, and postpartum periods by leveraging existing healthcare settings that serve women and couples at high risk of HIV-1 acquisition. These opportunities include integration of HIV-1 prevention strategies within antenatal and postnatal care programs in settings with high HIV-1 prevalence and inclusion of safer conception programs within clinical HIV-1 care for HIV-1 affected individuals and couples desiring children. Specifically, antiretrovirals, as PrEP used by HIV-1 uninfected people and ART used by HIV-1 infected people, are highly effective and important for women and couples, especially those planning and experiencing pregnancy. The aims within this dissertation address questions regarding HIV-1 risk and implementation of antiretrovirals for HIV-1 prevention among women and their partners during reproductive stages, including: quantifying the risk of female HIV-1 acquisition in different reproductive stages, making the case for PrEP as a highly efficacious HIV-1 strategy for women, and describing fertility intentions and willingness to use safer conception strategies during pregnancy attempts among HIV-1 infected individuals.

Previous studies have shown that pregnancy and postpartum are periods with heightened HIV-1 acquisition risk for women, but it is not clear whether this is primarily driven by biological or behavioral factors. We have addressed this gap by using robust data from two longitudinal studies to estimate the per coital act probability of female HIV-1 acquisition during the early pregnancy, late pregnancy, and postpartum stages, relative to time periods to unrelated to pregnancy. We found that the risk of HIV-1 transmission per coital act steadily increased pregnancy and was highest during postpartum, even after accounting for sexual behavior, PrEP, and HIV-1 viral load, suggesting that biological changes during these periods increase HIV-1 risk.

Conflicting results and conclusions from the initial randomized clinical trials that assessed efficacy of PrEP for HIV-1 prevention among women has spurred debate about whether PrEP is a strategy that women will use effectively. This debate has delayed the initiation of programs to deliver PrEP to women, and specifically has been a barrier to the integration of PrEP into antenatal and postnatal care where it has the potential to reach women who most need enhanced HIV-1 prevention. We have objectively assessed and synthesized existing evidence of PrEP efficacy among women and made a conclusive case that PrEP is an effective HIV-1 prevention strategy for women.

Couples affected by HIV-1 with fertility desires experience heightened vulnerability to HIV-1 acquisition when they forgo condom use during pregnancy attempts. “Safer conception” is a risk reduction approach where HIV-1 serodiscordant couples use one or more strategies to reduce the risk of HIV-1 transmission and optimize fertility during pregnancy attempts. We have contributed to the growing demand for information on safer conception with a cross-sectional study to describe fertility intentions and preferences for safer conception strategies, including PrEP and ART, among HIV-1 infected individuals in Seattle, WA.

The collective results from this dissertation provide evidence for the urgent need to enhance HIV-1 prevention during pregnancy and the postpartum period, and advance global and local delivery mechanisms for PrEP and ART during periods of heightened risk when they can have substantial HIV-1 prevention impact.

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DEDICATION

This work is dedicated to past and future generations of my family.

For my father, William A. Thomson Jr.
While our time together was short, your memory and strong civic duty
continuously fuels my commitment to public health prevention and public service.

– and –

For my children,
whose innocence and exuberance motivates me to improve
the health of our communities and optimize maternal and infant health.

CHAPTER 1: Introduction

Over the past two decades, considerable progress has been made in reducing HIV-1 related morbidity and mortality through expansion of antiretroviral therapy (ART) for HIV-1 affected individuals, yet an efficacious HIV-1 vaccine for HIV-1 uninfected individuals and cure for HIV-1 infected individuals have not yet been achieved. In this context, existing effective biomedical HIV-1 prevention strategies play a key role in reducing the number of new HIV-1 infections and achieving the ambitious goal of eliminating HIV/AIDS by the year 2030.

To contribute toward this goal, the current dissertation focuses on the need for and delivery of HIV-1 prevention for women of reproductive age, a population with high HIV-1 incidence, especially during time periods related to pregnancy. Specifically, work within this dissertation 1) quantifies the risk of HIV-1 acquisition by women during pregnancy and postpartum, 2) reviews the efficacy of pre-exposure prophylaxis (PrEP) for preventing female HIV-1 acquisition, and 3) assesses the acceptability of antiretroviral-based prevention among heterosexual HIV-1 infected individuals with fertility desires. Integration of HIV-1 prevention into routine services that reach populations at high risk of HIV-1 acquisition is both efficient and cost-effective. Our results highlight the importance of enhancing HIV-1 prevention, including delivery of ART and PrEP during pregnancy and the postpartum period, which have heightened vulnerability for women.

Women bear a great burden of the HIV-1 epidemic and are a priority population for new approaches to prevent heterosexual HIV-1 acquisition and onward transmission of HIV-1. HIV-1 is the leading cause of death worldwide among women of reproductive age [1]. In the high HIV-1 burden countries of sub-Saharan Africa, women represent 56% of new adult HIV-1 infections [2]. In the United States (US), women comprise only 25% of all HIV-1 infections, but women who belong to racial minority and lower socioeconomic groups are disproportionally affected by HIV-1 [1, 3, 4]. Women are at high risk for HIV-1 acquisition due to a complex combination of biological, behavioral, and cultural factors, including physiology of the female reproductive tract, prevalence of other sexually transmitted infections, poverty, violence, and limited access to and control over prevention strategies that rely on male partner involvement [1, 3, 5-8].

Risk of HIV-1 Acquisition during Pregnancy and Postpartum: Chapter 2

Are women at increased risk of HIV-1 acquisition during pregnancy and postpartum?

An important hypothesis to explain the increased risk of HIV-1 acquisition among women of reproductive age is increased vulnerability before, during, and after pregnancy, physiological states that are uniquely experienced by women. In many settings with high HIV-1 prevalence, fertility rates are also high and women spend a significant proportion of their reproductive years pregnant or postpartum**.** Increased risk of female HIV-1 acquisition during periods related to pregnancy is detrimental to the health and well-being of women and their families, including onward perinatal transmission of undiagnosed incident HIV-infections. A 2014 meta-analysis calculated a pooled HIV-1 incidence rate from 19 cohorts of women in sub-Saharan African countries of 3.8 per 100 person-years (95% CI 3.0-4.6) during the pregnancy and postpartum period, an estimate that exceeds incidence rates observed in African populations at high risk for HIV-1, such as female sex workers (2.7 per 100 person-years) and HIV-1 serodiscordant couples (2.0-3.6 per 100 person-years) [9]. However, as highlighted in this same article, individual studies assessing the relationship between the pregnancy and postnatal periods and female HIV-1 acquisition risk have yielded conflicting results [9].

It is currently unclear whether the observed increase in HIV-1 risk is attributable to the behavioral or biological changes that accompany pregnancy. Biological changes that occur during pregnancy, including changes in systemic and mucosal immunity from high levels of progesterone, alterations in the balance of vaginal microbiota, and the presence of other sexually transmitted infections (STIs), have all been proposed as possible mechanisms that increase female susceptibility to HIV-1 [9-11]. Simultaneously, the sexual behaviors of women and their male partners often change when attempting to become pregnant (i.e. the peri-conception period), during pregnancy, and after birth, including the frequency of sex, condom use, and additional sexual partners. It is possible that decreased sexual frequency during the pregnancy and postpartum period may offset any increased biological risk in HIV-1

acquisition from pregnancy itself, a relationship that has been difficult to evaluate given the methods used in previous studies. Estimates of the probability HIV-1 transmission per coital act during pregnancy-related stages offer new epidemiological evidence to substantiate increased risk of HIV-1 acquisition during pregnancy and inform whether this increase in risk is due to biological or behavioral factors.

Only one prior study has explored the per coital act HIV-1 acquisition risk in pregnancy and postpartum periods, using data from the 1994-99 Rakai, Uganda community cohort of HIV-1 serodiscordant couples, and is limited by annual data collection on sexual activity, pregnancy, and HIV-1 status [10]. In Chapter 2, we use robust longitudinal data collected monthly or quarterly from women with known HIV-1 infected male partners to estimate the per coital act probability of female HIV-1 acquisition in early pregnancy, late pregnancy, postpartum, and non-pregnant stages. Our results provide evidence that the risk of female HIV-1 acquisition per coital act is significantly higher in late pregnancy and postpartum, relative to non-pregnant time, suggesting that biological changes unique to these states increase female HIV-1 susceptibility. These results underscore the importance of HIV-1 prevention, counseling, and testing in antenatal and postpartum care in high HIV-1 prevalence settings to prevent sexual transmission and identify acute maternal HIV-1 infections.

Tenofovir-based oral pre-exposure prophylaxis (PrEP) for HIV-1 prevention among women: Chapter 3

Is daily tenofovir-based pre-exposure prophylaxis (PrEP) an efficacious HIV-1 prevention strategy for women?

PrEP, a relatively new strategy where HIV-1 uninfected individuals use daily oral antiretrovirals to prevent HIV-1 acquisition, holds great promise as a female-controlled HIV-1 prevention tool. However, divergent results across five efficacy trials (Table 1) initially raised questions over PrEP efficacy and effectiveness for women, including whether women could use PrEP with sufficient adherence to achieve protection against HIV-1 infection [12-16]. In the initial years following the 2012 approval of PrEP by the United States Food and Drug Administration, this debate hindered implementation of PrEP delivery programs for women.

Table 1: Efficacy Results from Randomized Clinical Trials of pre-exposure prophylaxis (PrEP) among Heterosexual Women, Men and Couples				
Trial Name	**PrEP Agent**	**Study Population**	**Efficacy (ITT)**	**Adherence**
Partners PrEP Study	Oral FTC/TDF	Heterosexual couples: Kenya, Uganda	75%	81%
	Oral TDF		62%	81%
TDF2	Oral FTC/TDF	Heterosexual couples: Botswana	62%	81%
The Bangkok Tenofovir Study	Oral TDF	Male and female injection drug users	49%	67%
FEM-PrEP	Oral FTC/TDF	Women: Kenya, Tanzania, and South Africa	6%*	24%
VOICE	Oral FTC/TDF	Women: South Africa, Uganda, Zimbabwe	-4%*	28%
	Oral TDF		-49%*	29%
**Relative risk reduction was not statistically significant*				

HIV-1 acquired during the periconception, pregnancy, or postpartum periods is extremely consequential for women and their children. When integrated into routine antenatal care settings and programs serving HIV-1 serodiscordant couples, PrEP can play an important role in preventing HIV-1 acquisition during these periods of increased risk. An in-depth understanding of these clinical trial results and synthesis of conclusive evidence on PrEP efficacy among women is imperative for the HIV-1 prevention community to scale-up of PrEP as a public health strategy, especially during high-risk periods related to pregnancy.

In Chapter 3, we address this barrier by conducting a comprehensive and critical appraisal of evidence across clinical trials, as well as sub-group analyses and qualitative follow-up interviews with clinical trial participants, to synthesize study findings and identify characteristics that contributed to divergent results across studies. In addition, we draw upon results from recent pharmacokinetics studies and open-label demonstration projects to discuss the effectiveness of PrEP implementation outside of clinical trials and explain the interface between biological efficacy and behavioral adherence. Our review conclusively establishes the merit of PrEP for women at high risk of HIV-1 acquisition, and we highlight emerging strategies for PrEP implementation. This synthesis is a succinct reference for policy makers and public health practitioners as they design programs to deliver PrEP to women.

Fertility desires and safer conception strategies among people receiving HIV-1 care in Seattle, WA: Chapter 4

What are the fertility desires among heterosexual HIV-1 infected patients receiving HIV-1 care in Seattle, WA?

What are the preferred HIV-1 prevention strategies among those with fertility desires?

Reproductive age HIV-1 uninfected women in sexual partnerships with known HIV-1 infected men warrant specific attention for enhanced HIV-1 prevention during time periods related to pregnancy. These women face heightened HIV-1 risk when attempting to satisfy goals for pregnancy, forgoing condom use during the peri-conception period and condomless sex often continues during pregnancy when the contraceptive benefit of condoms is no longer needed. 'Safer conception' counseling, which includes provider-patient counselling and utilization of one of more HIV-1 risk reduction strategy during pregnancy attempts, is increasingly being recognized as an essential part of long term care for people living with HIV-1 and people with HIV-1 risk. Antiretroviral-based HIV-1 prevention, as ART and/or PrEP, can form the cornerstone of HIV-1 prevention strategies for women and men attempting pregnancy, as they permit pregnancy (unlike condom use), are safe to use during pregnancy attempts, and may be more accessible than more expensive safer conception options, such as medically assisted reproduction [17-20].

Although the field of safer conception has received increasing attention in settings with a high prevalence of HIV-1 serodiscordant couples, such as sub-Saharan Africa, there has been less focus on the HIV-1 prevention needs and safer conception preferences of people living with HIV-1 in the US. Specifically, HIV-1 uninfected men and women who want to have a biological child with an HIV-1 infected partner are one potential new target group for PrEP, however PrEP as a safer conception strategy has only recently been introduced. In Chapter 4, we present results from our study to assess fertility intentions, acceptability of, and preferences for safer conception strategies among HIV-1 infected patients receiving care at the publicly-funded HIV-1 Clinic in Seattle, WA. Our findings identify that provider initiated discussions on fertility desires were infrequent, yet a third of reproductive age participants desire at least one or more child in the future, suggesting that there may be prevention gaps for HIV-1 affected individuals and couples who want to attempt pregnancy.

Summary

This dissertation addresses HIV-1 risk and prevention strategies for populations and time periods when HIV-1 acquisition is elevated, including pregnant and postpartum women and members of HIV-1 serodiscordant couples who are attempting pregnancy. Our work provides robust evidence that the risk of female HIV-1 acquisition per coital act is significantly higher during pregnancy-related stages, substantiates that PrEP is a highly efficacious and promising HIV-1 prevention strategy for women, and demonstrates that HIV-1 infected individuals in Seattle, WA have fertility desires and are willing to integrate safer conception strategies into their lives. Collectively, our results highlight the need for enhanced prevention strategies and advanced implementation of PrEP before, during, and after pregnancy where it can have substantial global and local public health impact.

CHAPTER 2: Risk of HIV-1 Acquisition during Pregnancy and Postpartum

Increased risk of female HIV-1 acquisition throughout pregnancy and postpartum: a prospective per coital act analysis among women with HIV-1 infected partners

Kerry A. Thomson, MPH[1]
James Hughes, PhD, MS[2]
Jared Baeten, MD, PhD [1,3,4]
Connie Celum, MD, MPH[11,3,4]
Craig R. Cohen, MD, PhD[5]
Grace John-Stewart, MD, PhD, MPH[1,3,4]
James Kiarie, MBChB, MMed, MPH [3,6]
Nelly Mugo, MBChB, MMed, MPH [3 6]
Kenneth Ngure, PhD, MSc, MPH[3,6]
Renee Heffron, PhD, MPH[1,3]

For the Partners in Prevention HSV/HIV Transmission Study and Partners PrEP Study Teams*

Author affiliations: Department of Epidemiology[1], Biostatistics[2], Global Health[3], and Medicine[4], University of Washington, Seattle, USA; University of California, San Francisco, USA[5]; Moi University, Eldoret, Kenya[6]

* The Partners in Prevention HSV/HIV Transmission Study and Partners PrEP Study Teams are listed in the Notes Section.

Corresponding author:
Renee Heffron, 325 Ninth Avenue Box 359927, Seattle, WA, USA 98104
Phone: +12065203817
Fax: +12065203831
Email: rheffron@uw.edu

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Abstract

Background: Understanding the absolute and relative risk of HIV-1 acquisition during pregnancy and postpartum can inform HIV-1 prevention strategies for women.

Methods: We used a complementary log-log model and data from 2,751 HIV-1 serodiscordant couples to compare the probability of female HIV-1 acquisition per sex act by reproductive stage (early pregnancy, late pregnancy, postpartum, or non-pregnant).

Results: At total of 686 pregnancies were identified and 82 incident HIV-1 infections occurred. After adjustment for condom use, age, PrEP use, and HIV-1 viral load, the per act probability of HIV-1 acquisition was higher in late pregnancy (aRR 2.82, p=0.01) and postpartum (aRR 3.97, p=0.01) compared to non-pregnant periods. The HIV-1 acquisition probability per condomless sex act for a 25 year old woman not taking PrEP with an HIV-1 infected male partner with viral load of 10,000 copies/ml was 0.0011 (95% CI: 0.005, 0.0019), 0.0022 (95% CI: 0.0004, 0.0093), 0.0030 (95% CI: 0.0007, 0.0108), and 0.0042 (95% CI: 0.0007, 0.0177) in the non-pregnant, early pregnant, late pregnant, and postpartum periods, respectively.

Conclusion: The HIV-1 acquisition probability per sex act steadily increased through pregnancy and was highest during the postpartum period, suggesting that biological changes unique to these states increases female HIV-1 susceptibility.

Introduction

HIV-1 is the leading cause of death worldwide among women of reproductive age [1]. In high HIV-1 burden countries of sub-Saharan Africa women represent 56% of new adult HIV-1 infections [2]. In many high HIV-1 prevalence settings, fertility rates are also high and women spend a significant proportion of their reproductive years pregnant, postpartum, or breastfeeding. A recent meta-analysis calculated a pooled HIV-1 incidence rate among African women of 4.7 per 100 person-years during pregnancy and 2.9 during postpartum, estimates that exceed HIV-1 incidence among female sex-workers and HIV-1 serodiscordant couples [9]. One potential hypothesis for the high HIV-1 incidence among reproductive age women is increased susceptibility during and after pregnancy.

Some, but not all, epidemiological studies have observed increased risk of HIV-1 acquisition during pregnancy and postpartum, relative to non-pregnant time [10, 11, 21]. Physiological changes that accompany pregnancy, including alterations in systemic and mucosal immunity and shifts in the vaginal microbiome, offer mechanistic hypotheses to support increased HIV-1 risk [22-30]. Analyses of pregnancy as a risk factor are challenging because data on sexual behavior, which often fluctuates during the pregnancy and postpartum periods, require frequent measurement so that changes in sexual activity do not obscure potential increased biological risk of HIV-1 from pregnancy itself. A per-coital act analysis aims to quantify the probability of HIV-1 acquisition with each sex act, given exposure to HIV-1 through condomless sex [31-33]. A commonly cited estimate for the per coital act probability of heterosexual HIV-1 transmission is 0.001 (1 infection per 1,000 sex acts) [32], although this does not account for differences based on behavioral or biological characteristics, such as pregnant and non-pregnant periods and partner HIV-1 viral load.

Quantifying the absolute and relative risks of female HIV-1 acquisition during pregnancy and postpartum, as well as further insight into whether any increased risk is attributable to biological or behavioral changes, is critical to inform the scale-up of interventions to protect the health of women and their families. We aimed to assess differential risk in HIV-1 acquisition across reproductive stages by calculating the per-coital act probability of female HIV-1 acquisition in early pregnancy, late pregnancy, and postpartum and comparing these estimates to non-pregnant times.

Methods

Study Population

The current analysis includes data from HIV-1 uninfected women in seven African countries (Bostwana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia) followed for up to 48 months in two randomized clinical trials between 2004 and 2013 [13, 34-37]. The Partners in Prevention HSV/HIV Transmission Study evaluated the efficacy of daily acyclovir HSV-2 suppressive therapy to prevent HIV-1 transmission; there was no significant difference between the intervention and placebo groups (hazard ratio: 0.92, p=0.69) [34]. The Partners PrEP Study evaluated the efficacy of daily oral pre-exposure prophylaxis (PrEP) to prevent HIV-1 acquisition; the reduction in HIV-1 acquisition was 67% (p<0.001) and 75% (p<0.001) in the tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC)/TDF arms, relative to placebo [13]. In both studies, women were ≥18 years of age and in stable partnerships with men known to be HIV-1 infected and not eligible for ART at enrollment.

Data Collection

Demographic and sexual behavior data were collected in both studies via standardized interviewer-administered case report forms in either English or local languages. In the Partners PrEP Study HIV-1 uninfected female attended monthly visits and their HIV-1 infected male partner attended quarterly visits. In the Partners in Prevention HSV/HIV Transmission Study HIV-1 uninfected female attended quarterly visits and their HIV-1 infected male partner attended monthly visits. HIV-1 RNA viral load was measured in women's HIV-1 infected partners at enrollment and then every six months in the Partners in Prevention HSV/HIV Transmission Study and annually in the Partners PrEP Study.

Assessment of HIV-1 Status

Women underwent monthly HIV-1 rapid testing in the Partners PrEP Study and quarterly in the Partners in Prevention HSV/HIV Transmission Study using two parallel HIV-1 antibody tests and positive results were confirmed by HIV-1 enzyme-linked immunoassay. HIV-1 acquisition events were classified as 'genetically linked' (i.e. likely transmitted from the male study partner) based on analysis of HIV-1 *env*

and *gag* or *pol* sequencing [38, 39]. In the event of an HIV-1 seroconversion, archived plasma specimens, collected at enrollment and every quarterly visit thereafter, were tested for HIV-1 RNA to determine the first evidence of infection.

Pregnancy Procedures

HIV-1 uninfected women enrolled in Partners in Prevention HSV/HIV Transmission Study could be pregnant at enrollment and had urine pregnancy tests when clinically indicated during follow-up (e.g. missed menses). HIV-1 uninfected women enrolled in the Partners PrEP Study were not pregnant at enrollment and had monthly urine pregnancy testing; study drug was withheld during pregnancy and breastfeeding [17]. Estimated date of delivery (EDD), last menstrual period (LMP), pregnancy end, and pregnancy outcome were collected for each identified pregnancy. We defined pregnancy start date as LMP and pregnancy end date as self-reported date of delivery or loss, with dates left censored at enrollment or right censored at study exit to capture time with data on sexual activity. Complete data on LMP and pregnancy end was available for 97% of pregnancies. For pregnancies with incomplete dates (3%), we assigned pregnancy start and/or end dates based a combination of pregnancy outcome, reported pregnancy duration, LMP, and/or EDD.

Statistical Analysis

Pregnancy incidence was calculated as the number of pregnancies per 100 person years when women were not pregnant. HIV-1 incidence was calculated as the number of genetically 'linked' new HIV-1 infections per 100 person years. First evidence of HIV-1 infection was defined as the earliest date of positive HIV-1 antibody test or HIV-1 RNA detected in archived plasma. Visits were censored once the male partner reported initiation of ART. Women who had HIV-1 RNA detected at enrollment were excluded from the analysis. Women who acquired HIV-1 that was not genetically linked to their male study partner were censored at the visit prior to first evidence of HIV-1 infection.

Reproductive stage was assessed as a time-varying exposure in all models. Start and end dates for each pregnancy were used to calculate the number of days within each interval between HIV-1 tests that were in: 1) early pregnancy (pregnancy start to 13 weeks gestation), 2) late pregnancy (14 weeks to

pregnancy end), 3) postpartum (delivery to 24 weeks for livebirths) or 4) non-pregnant (i.e. not pregnant nor postpartum). The proportion of each HIV-1 testing interval spent across the four reproductive stages was calculated as the number of days spent in each stage divided by the total number of days elapsed between HIV-1 tests. The total proportion across reproductive stages per interval was equal to one; women in a pregnancy-related state could spend time in more than one stage per HIV-1 testing interval and for women who were not pregnant during follow-up all study time was categorized as 'non-pregnant.' The maximum duration of risk, early pregnancy through postpartum, for a live birth was 64 weeks. In cases of contiguous pregnancies, the postpartum period was truncated to allow study time to reflect the early pregnancy state in the subsequent pregnancy. Women who experienced a pregnancy loss were assigned postpartum time based on expected return to ovulation: pregnancy loss <6 weeks: no postpartum time [40]; pregnancy loss between 6-20 weeks: 28 days [41, 42]; pregnancy loss ≥20 weeks or infant death before six months: 42 days [43, 44]. To calculate HIV-1 incidence by reproductive stage, events were assigned to the stage the woman was in at first evidence of HIV-1 infection.

To determine the number of sex acts associated with each HIV-1 testing interval, women's monthly reports of sex acts with their study partners were used from the Partners PrEP Study and men's monthly report of sex acts with their study partners, aggregated over the three months between women's HIV-1 tests, were used from the Partners in Prevention HSV/HIV Transmission Study. In instances where > 6 weeks elapsed between visits (2.6% of all visits), missing data on sex acts were imputed based on the mean of monthly sex acts reported at previous visits multiplied by the number of month(s) missed. Rates of sexual activity were calculated as the number of reported sex acts, with and without a condom, per person-month in each reproductive stage. To compare the frequency of sexual behavior across reproductive stages, we fit Poisson regression models with an independent correlation matrix and robust standard errors. *A priori*, we adjusted these models for female age and relationship duration.

To estimate the per-coital act probability of HIV-1 acquisition per condomless sex act we used a complementary log-log model [$p(X;n) = 1 - (1-\lambda)^{ne^{x\beta}}$] where λ is the per-coital act infectivity, *n* is the cumulative number of sexual acts reported in a given HIV-1 testing interval, *X* are covariates (including, specifically, the proportion of time spent in each reproductive stage and the proportion of sex acts protected by a condom in the current interval), and *p(X;n)* is the overall probability of HIV-1 acquisition by

the HIV-1 uninfected woman from her HIV-1 infected male partner [33]. HIV-1 acquisition was a rare event; for small values of λ, the β-coefficient of each reproductive stage represents the log relative risk of acquisition for that reproductive stage.

The adjusted model included time-varying covariates for the HIV-1 plasma viral load of the male partner (carried forward between measurements [45]) and female use of active PrEP (based on arm and monthly dispensation records) due to their known influence on HIV-1 transmission. We assessed additional demographic and clinical variables as potential confounders and included variables that changed the risk estimate for any reproductive stage by ≥10% in the adjusted model. HIV-1 viral load was centered at 10,000 copies/ml and female age was centered at 25 years. Thus, the reference case for adjusted absolute HIV-1 acquisition probabilities was a condomless sex act between a 25 year old woman not using PrEP and a male partner with HIV-1 RNA of 10,000 copies/ml.

To evaluate the robustness of our findings we conducted four sensitivity analyses. 1) Given PrEP efficacy for HIV-1 prevention, we excluded women randomized to the active arms of the Partners PrEP Study. 2) To address any potential bias from using male report of sex acts we used female report of sex acts for participants in Prevention HSV/HIV Transmission Study, calculated as the monthly report multiplied by three to account for data not collected between quarterly visits. 3) To address any residual or unmeasured confounding that may result from differences between those who did and did not become pregnant we excluded women with no study pregnancies. 4) To assess the impact of missing data we excluded any visit where sex acts were imputed.

All data were analyzed using SAS version 9.4. The protocols for each study were approved by the Human Subjects Division at the University of Washington and ethics review committees for each study site. All participants provided written informed consent.

Results

The current analysis included 2,751 HIV-1 uninfected women ages 18-49 who completed at least one follow-up visit before their HIV-1 infected partner initiated ART. In the month prior to enrollment, the median number of sex acts within study partnerships was 4.0 (IQR 2.0-8.0) and a quarter (24.4%) reported at least one condomless sex act with their study partner (Table 2).

A total of 5,069 person-years were accrued and median duration of follow-up was 23.5 months (IQR 13.9-29.8) per woman. The rate of total sex acts within the study partnership was 4.62, 4.71, 3.24, and 2.32 per person-month in non-pregnant, early pregnancy, late pregnancy, and postpartum periods, respectively (Table 3). After adjusting for age and relationship duration, compared to non-pregnant periods average sex frequency was significantly lower during late pregnancy (aRR 0.66, $p<0.0001$) and postpartum (aRR 0.45, $p<0.0001$) and average frequency of condomless sex with study partners was significantly higher during early pregnancy (aRR 2.43, $p<0.0001$).

Nearly a quarter of women (22.4%) experienced at least one pregnancy during follow-up (Table 4), of whom 89.4% had one pregnancy, 9.9% had two pregnancies, and 0.3% had three and four pregnancies each. Ninety-two women were pregnant at enrollment and 594 pregnancies were identified during follow-up. The pregnancy incidence rate was 12.50 per 100 person-years (95% CI: 11.52-13.55). Of the total 686 pregnancies, 62.1% ended with a live birth, 24.6% resulted in a pregnancy loss, and 13.3% of pregnancies were ongoing at study exit.

Eighty-two genetically linked HIV-1 events were observed for an overall (linked) HIV-1 incidence rate of 1.62 per 100 person-years (95% CI: 1.29-2.01) (Table 5). For 24 HIV-1 events, the first evidence of HIV-1 infection was detected at a study visit that occurred during the early pregnancy through postpartum periods. HIV-1 incidence per 100 person-years was 1.25 during non-pregnant study time (95% CI: 0.95, 1.62), 3.75 during early pregnancy (95% CI: 1.22, 8.75), 7.02 during late pregnancy (95% CI: 3.74 12.01), and 4.68 during postpartum (95% CI: 1.72, 10.18).

Table 6 presents estimated HIV-1 acquisition probabilities per condomless sex act. In the base model that included total sex acts and the proportion of the acts protected by a condom, HIV-1 acquisition rates per condomless sex act were significantly higher in each pregnancy-related stage relative to time non-pregnant time. After adjustment for age, use of PrEP, and HIV-1 viral load of the male partner, the probability of HIV-1 acquisition was significantly higher throughout pregnancy and postpartum (aRR 2.76 , 95% CI: 1.58-4.81). This increase was driven by the late pregnancy (aRR 2.82, 95% CI: 1.29-6.15, $p=0.01$) and postpartum (aRR 3.97, 95% CI: 1.50-10.51, $p=0.01$) periods. The HIV-1 acquisition probability for the reference case per 1,000 sex acts was 1.05. 2.19, 2.97, and 4.18 in non-pregnant, early

pregnancy, late pregnancy, and postpartum periods, respectively (Figure 1). The relationship between male partner HIV-1 viral load and HIV-1 acquisition probability was consistently linear within each reproductive stage (Figure 2).

The results of the adjusted model remained stable in sensitivity analysis. The probability of HIV-1 acquisition per act was significantly higher during pregnancy-related (combined) vs. non-pregnant time periods when 1) women randomized to the active arms of the Partners PrEP Study were excluded (aRR 2.92, p=0.001); 2) only sex acts reported by females were used (aRR 2.37, p=0.003); 3) women who never became pregnant during follow-up were excluded (aRR 3.37, p=0.002); and 4) all visits where sex acts were imputed were excluded (aRR 3.11, p=0.0002).

Discussion

In this prospective study, the risk of female HIV-1 acquisition per condomless sex act was three and four-fold higher during the late pregnancy and postpartum stages, respectively, results that remained significant after adjustment for factors known to effect HIV-1 acquisition. These findings underscore the need for continued counselling on HIV-1 risk and options for enhanced HIV-1 prevention for women during pregnancy and postpartum periods. To our knowledge, this is the first study to estimate HIV-1 acquisition probabilities disaggregated by early pregnancy, late pregnancy, postpartum, and non-pregnant periods. An additional use for these results is to parameterize mathematical models that forecast the impact and cost-effectiveness of HIV-1 interventions among populations with high pregnancy rates.

Our results suggests that biological factors unique to pregnancy increase female HIV-1 susceptibility. Estrogen and progesterone levels steadily increase and remain high throughout pregnancy, relative to a non-pregnant state [46]. These hormonal shifts induce a cascade of synergistic changes within the female genital tract (FGT), including increased inflammation, decreased integrity of the vaginal epithelium, and alterations in vaginal microbiota, all of which have been associated with increased HIV-1 susceptibility. Pregnancy activates innate immunity, increasing inflammation and HIV-1 target cells in the FGT [22, 27], while simultaneously suppressing adaptive immunity and reducing natural killer cells, changes that can persist as long as nine months after delivery [23-25]. Results from animal, ex vivo, and

human epidemiological studies have demonstrated that such immune activation and the ensuing inflammation are associated with increased risk of HIV-1 acquisition [28-30, 47]. Our finding that overall sexual frequency declines during pregnancy and postpartum is consistent with results from similar populations [48-50]. However in other studies many African women report resuming sexual activity within six to eight weeks after delivery [48, 51-54]. An additional potential mechanism for the increased risk we observed during the postpartum period is macro- and micro-trauma, caused by vaginal delivery or vaginal dryness from low levels of estrogen during breastfeeding, which reduce the integrity of the vaginal epithelium and creates a more conducive environment for HIV-1 acquisition. Although the sexually transmitted infection (STI) status of either partner, including HSV-2, was not a confounder in the current analysis, STIs are a risk factor for HIV-1 acquisition [55-57], including during pregnancy [58], and the prevalence of vaginal infections among pregnant and postpartum women in other populations has been high, positing another biological hypothesis for why pregnancy periods could induce greater susceptibility to HIV-1 [59-63].

A study from Rakai, Uganda estimated the per coital act of female HIV-1 acquisition risk among HIV-1 serodiscordant couples during pregnancy (0.0013) and breastfeeding (0.0009), but found no significant difference between these periods relative to non-pregnant periods (0.0007, aRR=1.42, 95% CI: 0.37, 3.82) [10]. However, annual data collection in this community cohort may have resulted in misclassification of dates for HIV-1 infection or pregnancy and inaccurate recall of sexual activity. In contrast, data used in the current analysis included more than 5,000 years of follow-up from 2,751 HIV-1 uninfected women in which sexual activity was reported monthly and women were tested frequently for both HIV-1 and pregnancy, methods that facilitated precise classification of sex acts, pregnancy dates, and HIV-1 status [31, 32, 64]. Furthermore, we were able to account for partner characteristics with restriction to genetically linked incident HIV-1 infections and time-varying adjustment for the partner's HIV-1 viral load. Sexual activity, including frequency and condom use, was subject to self-report and it is unknown how pregnancy status may have affected the accuracy of this reporting. A previous simulation study suggests that over-reporting of condom use would not significantly alter estimates for our reproductive stage covariates in a per-act analysis [64]. Reassuringly, our finding of increased risk was consistent across four sensitivity analyses that addressed potential confounding or misclassification.

These results have a number of public health implications for integration of HIV-1 prevention strategies into existing reproductive health services. As a highly efficacious [13-15, 65-68], cost-effective [69-71], female-controlled strategy, daily tenofovir-based oral PrEP can play an important role in preventing HIV-1 acquisition during pregnancy and postpartum, especially for women who are unable to engage their male partner(s) in HIV-1 prevention. Available safety data indicate that maternal tenofovir use is not associated with an increase in adverse birth or infant outcomes and infants are exposed to low levels of tenofovir through breastmilk [72-74]. This body of evidence has resulted in WHO guidelines that promote PrEP use for pregnant and breastfeeding women at high risk of HIV-1 acquisition [19, 20, 74-77]. Decisions about PrEP use during reproductive periods must carefully evaluate the potential risks and benefits, taking into consideration that individual cumulative risk will vary based on the duration of time pregnant or breastfeeding and the frequency of exposure through condomless sex with an HIV-1 infected partner. Use of PrEP during pregnancy has been an acceptable risk-reduction strategy for women with partners who are known to them to be HIV-1 infected [78]. Ongoing and planned studies will assess delivery models for PrEP within routine maternal and child health services [79, 80].

Integrating additional HIV-1 testing in antenatal and postpartum care, specifically male partner testing and repeat maternal testing, are opportunities to identify women at increased risk of HIV-1 acquisition or undiagnosed HIV-1 infection. Women with male partners of unknown HIV-1 status may be unaware of the need for HIV-1 prevention during pregnancy and postpartum [58]. Innovative approaches such a home-based couples testing [81-84] and secondary distribution of self-test kits from pregnant women to their partners [85, 86] have increased male acceptability of HIV-1 testing and identification of HIV-1 serodiscordant couples [87]. WHO recommends at least one repeat HIV-1 test during pregnancy, labor, or postpartum for women living in generalized HIV-1 epidemics [88], however these guidelines lack specificity in terms of when to test and are inconsistently implemented [89]. In a recent study, 68.7% of 173 hospitalized HIV-1 infected children were born to mothers that had not been tested or who had a previous negative HIV-1 test result during pregnancy, highlighting HIV-1 seroconversions that occurred later in pregnancy/postpartum and were undetected in the absence of repeat testing [90]. Specific normative guidance on repeat maternal testing is urgently needed, followed by strategies that integrate testing into maternal care, especially during the postpartum period which our study identified as having

the highest per-act risk of HIV-1 acquisition and can be accompanied by increased risk of perinatal transmission through breastmilk from acute HIV-1 infection [91].

Conclusion

This study provides strong evidence that the risk of HIV-1 acquisition per sex act steadily increases throughout pregnancy and is highest during postpartum. While further research is needed to better understand biological susceptibility that accompanies these periods, scale-up of HIV-1 prevention, counseling, and testing in antenatal and postpartum care in high HIV-1 prevalence settings is warranted to prevent sexual transmission and identify acute maternal HIV-1 infections.

Table 2: Enrollment Characteristics of 2,751 African Women with an HIV-1 Infected Male Partner, Median (IQR) or Frequency (%)		
	N=2,751 couples	
	Characteristics of the HIV-1 uninfected women	Characteristics of the HIV-1 infected male partners
Individual characteristics		
Age (years)	32.0 (27.0-37.7)	37.6 (32.7-43.1)
Education (years)	7.0 (4.0-9.0)	7.0 (5.0-11.0)
Effective contraceptive use†	1,050 (38.0)	--
Medical characteristics		
Circumcised	--	919 (33.2)
Sexually transmitted infection‡	856 (30.9)	222 (8.0)
HSV-2 seropositive	2,240 (82.2)	1,167 (42.4)**
Couple characteristics*		
Partnership duration (years)	9.7 (4.4-16.6)	
Married to study partner	2,547 (92.1)	
Living together	2,667 (96.4)	
Number of living children with study partner	2.0 (1.0-4.0)	
Sexual behavior in previous 30 days		
Number of sex acts with study partner	4.0 (2.0-8.0)	4.0 (2.0-8.0)
Number of sex acts with study partner protected by a condom	3.0 (1.0-6.0)	3.0 (2.0-6.0)
Any condomless sex with study partner	670 (24.4)	706 (25.7)
Any sex acts with additional partner	12 (0.4)	339 (12.3)
Clinical characteristics of HIV-1 infected partner		
Plasma HIV-1 RNA viral load (log_{10} copies / mL)	--	4.2 (3.5-4.8)
CD4 count (cells/mm^3)	--	447.0 (347.0-584.0)

†Includes: implants, injectable, oral contraceptive pills, intrauterine device, and permanent methods
‡ Laboratory diagnosis of Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum, Trichomonas vaginalis, HSV2, or bacterial vaginosis (females only)
**Couple characteristics reported by the HIV-1 uninfected female*
***Includes missing data (not tested in denominator, baseline data available from 298+1,021 HIV-1 infected men (48%) included in analysis*

Table 3: Sexual Activity During Study Follow-up by Reproductive Stage among 2,751 African Heterosexual HIV-1 Serodiscordant Couples with a HIV-1 Uninfected Female Partner				
Reproductive Stage*	Non-pregnant / non-postpartum	Early Pregnancy	Late Pregnancy	Postpartum
Total sex acts reported with study partner	256,462	7,548	7,205	3,573
Total condomless sex acts reported with study partner	25,946	1,530	947	327
Total person-months during follow-up	55,504	1,602	2,224	1,541
Rate of sex acts with study partner per person-month	4.62 (4.60, 4.64)	4.71 (4.61, 4.82)	3.24 (3.17, 3.32)	2.32 (2.24, 2.40)
Crude Relative Risk for Mean Sex Act (95% CI, p-value)	1.00	1.11 (1.01, 1.21) 0.02	0.70 (0.63, 0.78) < 0.0001	0.48 (0.42, 0.55) < 0.0001
Adjusted† Relative Risk for Mean Sex Act (95% CI, p-value)	1.00	1.04 (0.95, 1.14) 0.40	0.66 (0.59, 0.73) < 0.0001	0.45 (0.39, 0.51) < 0.0001
Rate of condomless sex acts with study partner per person-month	0.47 (0.46, 0.47)	0.96 (0.91, 1.00)	0.43 (0.40, 0.45)	0.21 (0.19, 0.24)
Relative Risk for Mean Condomless Sex Act (95% CI, p-value)	1.00	2.64 (2.10, 3.31) <0.0001	0.97 (0.70, 1.32) 0.83	0.55 (0.29, 1.04) 0.07
Adjusted† Relative Risk for Mean Sex Act (95% CI, p-value)	1.00	2.43 (1.91, 3.10) <0.0001	0.91 (0.66, 1.25) 0.55	0.51 (0.27, 0.97) 0.04

**Early pregnancy defined as pregnancy start (typically last menstrual period) to 13 weeks. Late pregnancy defined as 14 weeks to pregnancy end. Postpartum defined as pregnancy end until six months postpartum (live birth), until six weeks postpartum (pregnancy loss ≥ 20 weeks or newborn death) or until 4 weeks postpartum (pregnancy loss 6-19 weeks).*

† Adjusted for female age and duration of relationship with HIV-1 infected study partner

Table 4: Pregnancy Incidence and Outcomes among 2,751 African Heterosexual HIV-1 Serodiscordant Couples with a HIV-1 Uninfected Female Partner, Median (IQR) or Frequency (%)	
Number of women ever pregnant during follow-up	615 (22.4)
Total person-years of follow-up	5,069
Total person-years pregnant	318
Total person-years at risk of pregnancy	4,751
Total pregnancies	686
Pregnancy identified at enrollment	92 (13.4)
Incident pregnancy identified during follow-up	594 (86.6)
Pregnancy incidence rate per 100 person-years	12.50 (11.52, 13.55)
Pregnancy outcomes	
Pregnant at study exit	91 (13.3)
Live birth	426 (62.1)
Any Pregnancy loss	169 (24.6)
Loss < 6 weeks	29 (17.2)
Loss at 6-13 weeks	97 (57.4)
Loss at 14-19 weeks	24 (14.2)
Loss at 20+ weeks	19 (11.2)

Table 5: Male to Female HIV-1 Incidence Rates by Reproductive Stage† among 2,751 African Heterosexual HIV-1 Serodiscordant Couples

	Combined data for manuscript	
Reproductive stage	HIV-1 seroconversions / person-years	HIV-1 incidence rate per 100 person-years (95% CI)
Total	82 / 5,069	1.62 (1.29, 2.01)
During non-pregnant/postpartum time	58 / 4,622	1.25 (0.95, 1.62)
During early pregnancy through postpartum	24 / 447	5.37 (3.44, 7.99)
During early pregnancy*	5 / 133	3.75 (1.22, 8.75)
During late pregnancy *	13 / 185	7.02 (3.74, 12.01)
During postpartum*	6 / 128	4.68 (1.72, 10.18)

† Reproductive stage determined by stage at the study visit when first evidence of HIV-1 was identified

*Early pregnancy defined as pregnancy start (typically last menstrual period) to 13 weeks. Late pregnancy defined as 14 weeks to pregnancy end. Postpartum defined as pregnancy end until six months postpartum (live birth), until six weeks postpartum (pregnancy loss ≥ 20 weeks or newborn death) or until 4 weeks postpartum (pregnancy loss 6-19 weeks).

Table 6: Female HIV-1 Acquisition Probabilities and Relative Risk of HIV-1 Acquisition by Reproductive Stage among 2,751 African Women with HIV-1 Infected Male Partners

	Base Model†			Adjusted Model††		
	Probability of HIV-1 acquisition per condomless sex act (95% CI)	Relative Risk¶ for per-act probability of HIV-1 acquisition (95% CI)	p-value	Probability§ of HIV-1 acquisition per condomless sex act (95% CI)	Relative Risk¶ for per-act probability of HIV-1 acquisition (95% CI)	p-value
During early pregnancy through postpartum	0.0027 (0.0009, 0.0074)	4.97 (2.95, 8.38)	<0.001	0.0029 (0.004, 0.0093)	2.76 (1.58, 4.81)	<0.001
During early pregnancy*	0.0018 (0.0003, 0.0070)	3.20 (1.24, 8.25)	0.02	0.0022 (0.0004, 0.0093)	2.07 (0.78, 5.49)	0.14
During late pregnancy *	0.0031 (0.0008, 0.0102)	5.54 (2.62, 11.69)	<0.001	0.0030 (0.0007, 0.0108)	2.82 (1.29, 6.15)	0.01
During postpartum*	0.0044 (0.0008, 0.0167)	7.80 (3.04, 20.02)	<0.001	0.0042 (0.0007, 0.0177)	3.97 (1.50, 10.51)	0.01
During non-pregnant / non-postpartum time	0.0005 (0.0003, 0.0009)	1.00	--	0.0011 (0.005, 0.0019)	1.00	--

†Base model adjusted for condom use and reproductive stage

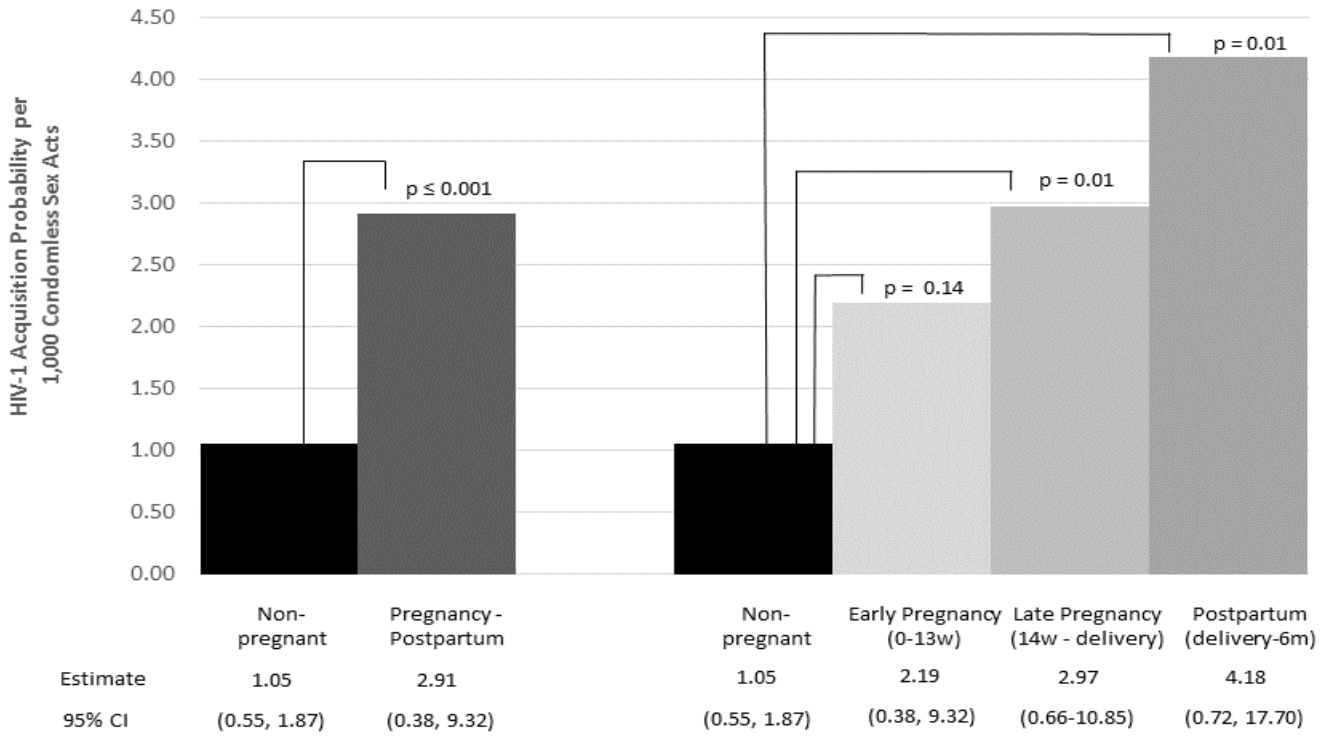
††Adjusted for condom use, reproductive stage, male partner viral load female age, and on active pre-exposure prophylaxis (PrEP) for women randomized to and dispensed active PrEP in the Partners PrEP study

§ Adjusted absolute female HIV-1 acquisition probabilities represent infectivity estimates per condomless sex act with an HIV-1 infected partner with viral load of 10,000 copies/ml for a 25 year old female not taking pre-exposure prophylaxis (PrEP).

¶ The reference group for the adjusted model represents a condomless sex act with an HIV-1 infected partner with viral load of 10,000 copies/ml for a 25 year old female not taking pre-exposure prophylaxis (PrEP) occurring while the woman is not pregnant or postpartum.

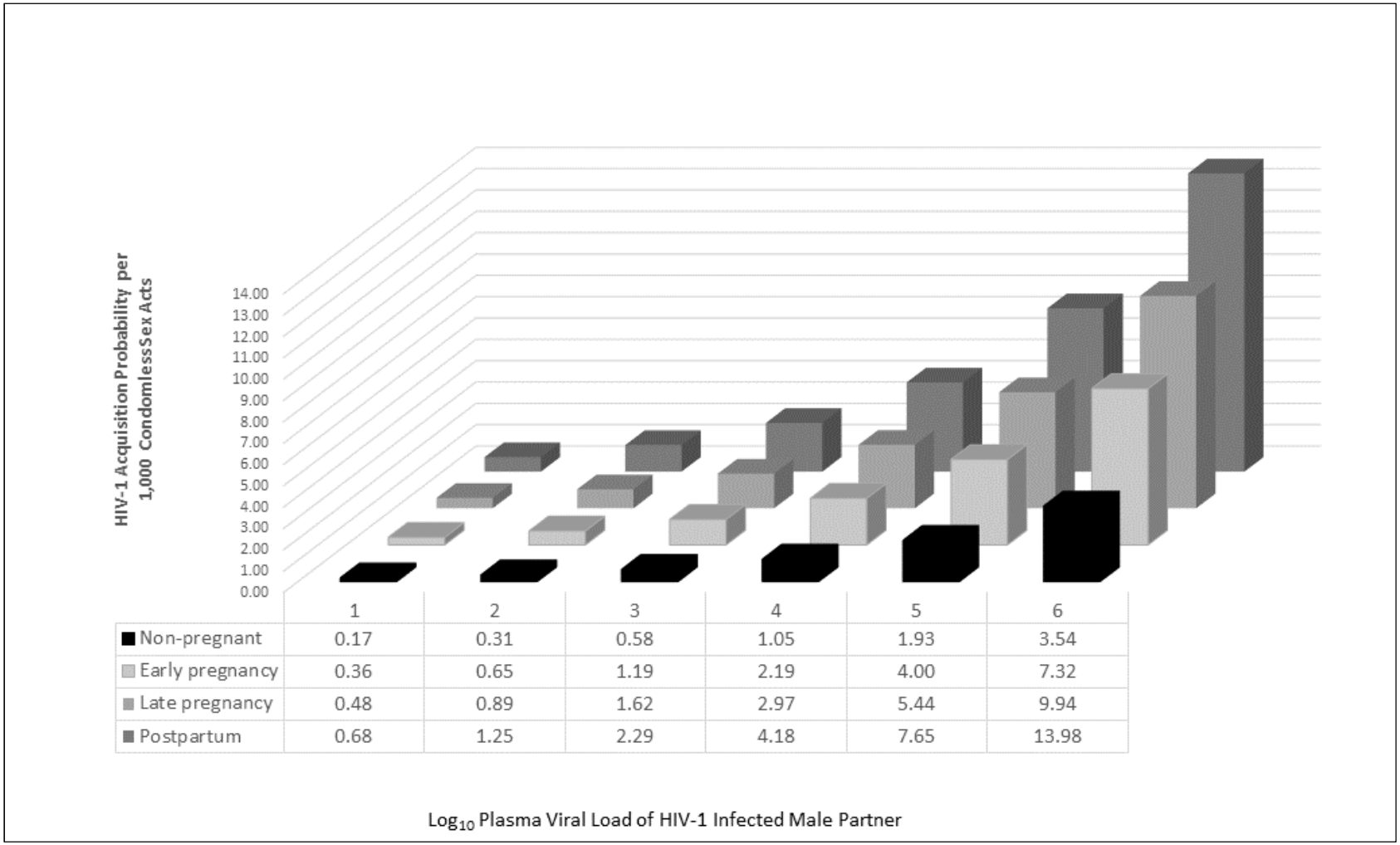
*Early pregnancy defined as pregnancy start (typically last menstrual period) to 13 weeks. Late pregnancy defined as 14 weeks to pregnancy end. Postpartum defined as pregnancy end until six months postpartum (live birth), until six weeks postpartum (pregnancy loss ≥ 20 weeks or newborn death) or until 4 weeks postpartum (pregnancy loss 6-19 weeks).

Figure 1: Probability of Female HIV-1 Acquisition per 1,000 Condomless Sex Acts by Reproductive Stage



Caption for Figure 1: Adjusted absolute female HIV-1 acquisition probabilities represent infectivity estimates per 1,000 condomless sex acts with an HIV-1 infected partner with viral load of 10,000 copies/ml for a 25 year old woman not taking pre-exposure prophylaxis (PrEP).

Figure 2: Female HIV-1 Acquisition Probabilities by Reproductive Stage and male partner HIV-1 Viral Load



	1	2	3	4	5	6
Non-pregnant	0.17	0.31	0.58	1.05	1.93	3.54
Early pregnancy	0.36	0.65	1.19	2.19	4.00	7.32
Late pregnancy	0.48	0.89	1.62	2.97	5.44	9.94
Postpartum	0.68	1.25	2.29	4.18	7.65	13.98

Caption for Figure 2: Adjusted absolute female HIV-1 acquisition probabilities represent infectivity estimates per 1,000 condomless sex acts for a 25 year old woman not taking pre-exposure prophylaxis (PrEP) at varying level of HIV-1 viral load for a male HIV-1 infected partner.

Notes

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Partners in Prevention HSV/HIV Transmission Study Team. *University of Washington Coordinating Center and Central Laboratories*, Seattle, USA: Connie Celum (principal investigator), Anna Wald (protocol co-chair), Jairam Lingappa (medical director), Jared M. Baeten, Mary Campbell, Lawrence Corey, Robert W. Coombs, James P. Hughes, Amalia Magaret, M. Juliana McElrath, Rhoda Morrow, James I. Mullins.

***Study Sites and Site Principal Investigators*.** Cape Town, South Africa (University of Cape Town): David Coetzee; Eldoret, Kenya (Moi University, Indiana University): Kenneth Fife, Edwin Were; Gaborone, Botswana (Botswana Harvard Partnership): Max Essex, Joseph Makhema; Kampala, Uganda (Infectious Disease Institute, Makerere University): Elly Katabira, Allan Ronald; Kigali, Rwanda (Rwanda Zambia HIV Research Group, and Emory University): Susan Allen, Kayitesi Kayitenkore, Etienne Karita; Kisumu, Kenya (Kenya Medical Research Institute, University of California San Francisco): Elizabeth Bukusi, Craig Cohen; Kitwe, Zambia (Rwanda Zambia HIV Research Group, and Emory University): Susan Allen, William Kanweka; Lusaka, Zambia (Rwanda Zambia HIV Research Group, and Emory University): Susan Allen, Bellington Vwalika; Moshi, Tanzania (Kilimanjaro Christian Medical College, Harvard University): Saidi Kapiga, Rachel Manongi; Nairobi, Kenya (University of Nairobi, University of Washington): Carey Farquhar, Grace John-Stewart, James Kiarie; Ndola, Zambia (Rwanda Zambia HIV

Research Group, and Emory University): Susan Allen, Mubiana Inambao; Orange Farm, South Africa (Reproductive Health Research Unit, University of the Witwatersrand): Sinead Delany-Moretlwe, Helen Rees; Soweto, South Africa (Perinatal HIV Research Unit, University of the Witwatersrand): Guy de Bruyn, Glenda Gray, James McIntyre; Thika, Kenya (University of Nairobi, University of Washington): Nelly Rwamba Mugo

Partners PrEP Study Team. *University of Washington Coordinating Center and Central Laboratories*, Seattle, USA: Connie Celum (principal investigator, protocol co-chair), Jared M. Baeten (medical director, protocol co-chair), Deborah Donnell (protocol statistician), Robert W. Coombs, Jairam R. Lingappa, M. Juliana McElrath.

***Study Sites and Site Principal Investigators*.** Eldoret, Kenya (Moi University, Indiana University): Kenneth H. Fife, Edwin Were; Kabwohe, Uganda (Kabwohe Clinical Research Center): Elioda Tumwesigye; Jinja, Uganda (Makerere University, University of Washington): Patrick Ndase, Elly Katabira; Kampala, Uganda (Makerere University): Elly Katabira, Allan Ronald; Kisumu, Kenya (Kenya Medical Research Institute, University of California San Francisco): Elizabeth Bukusi, Craig R. Cohen; Mbale, Uganda (The AIDS Support Organization, CDC-Uganda): Jonathan Wangisi, James D. Campbell, Jordan W. Tappero; Nairobi, Kenya (University of Nairobi, University of Washington): James Kiarie, Carey Farquhar, Grace John-Stewart; Thika, Kenya (University of Nairobi, University of Washington): Nelly R. Mugo; Tororo, Uganda (CDC-Uganda, The AIDS Support Organization): James D. Campbell, Jordan W. Tappero, Jonathan Wangisi. Data management was provided by DF/Net Research, Inc. (Seattle, USA) and site laboratory oversight was provided by Contract Lab Services (University of the Witwatersrand, Johannesburg, South Africa).

CHAPTER 3: Tenofovir-based oral pre-exposure prophylaxis prevents HIV infection among women

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Tenofovir-based Oral PrEP Prevents HIV Infection among Women

Kerry A. Thomson, MPH[1, 2]
Jared M. Baeten, MD, PhD[1,2,3]
Nelly R. Mugo, MBChB, MMed, MPH[1,4]
Linda-Gail Bekker, MBChB, FCP, PhD[5]
Connie L. Celum, MD, MPH[1,2,3]
Renee Heffron, PhD, MPH[1,2]

Author affiliations: Departments of Global Health[1], Epidemiology[2], and Medicine[3], University of Washington, Seattle, USA; [4]Sexual Reproductive Adolescent and Child Health Program, Kenya Medical Research Institute, Nairobi, Kenya; [5]The Desmond Tutu HIV Centre, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Corresponding author:
Jared Baeten
Department of Global Health, University of Washington
325 Ninth Avenue, Box 359927
Seattle, WA 98104 USA
Phone: +1-206-520-3820
Fax: +1-206-520-3831
Email: jbaeten@uw.edu

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Abstract

Purpose of review: Despite tremendous promise as a female-controlled HIV prevention strategy, implementation of pre-exposure prophylaxis (PrEP) among women has been limited, in part because of disparate efficacy results from randomized trials in this population. This review synthesizes existing evidence regarding PrEP efficacy for preventing HIV infection in women and considerations for delivering PrEP to women.

Recent findings: In three efficacy trials, conducted among men and women, tenofovir-based oral PrEP reduced HIV acquisition in subgroups of women by 49-79% in intent-to-treat analyses, and by >85% when accounting for PrEP adherence. Two trials did not demonstrate an HIV prevention benefit from PrEP in women, but substantial evidence indicates those results were compromised by very low adherence to the study medication. Qualitative research has identified risk perception, stigma, and aspects of clinical trial participation as influencing adherence to study medication. Pharmacokinetic studies provide supporting evidence that PrEP offers HIV protection in women who are adherent to the medication.

Summary: Tenofovir-based daily oral PrEP prevents HIV acquisition in women. Offering PrEP as an HIV prevention option for women at high risk of HIV acquisition is a public health imperative and opportunities to evaluate implementation strategies for PrEP for women are needed.

Key words: HIV prevention, pre-exposure prophylaxis, women, efficacy, effectiveness, adherence

Introduction

HIV/AIDS is the leading cause of death among women of reproductive age, and a combination of biological, behavioral, and sociocultural factors result in women bearing a disproportionate burden of the global HIV epidemic [1, 92]. HIV prevention strategies available to women at risk of sexual transmission include abstinence from sexual activity, female and male condoms, and antiretroviral therapy (ART) use or voluntary male medical circumcision by their partners; however, all of these strategies depend on male partner cooperation. Tenofovir disoproxil fumarate (TDF)-based pre-exposure prophylaxis (PrEP) is a novel prevention strategy in which HIV uninfected individuals use an oral antiretroviral medication as chemoprophlaxis to reduce HIV acquisition [93]. PrEP holds tremendous promise as a female-controlled prevention approach, and international normative bodies recommend PrEP for persons at substantial HIV risk, including women [18-20, 75, 94]. Cost, policies, infrastructure, and limited availability of antiretroviral medications are logistical considerations limiting the scale-up of PrEP in areas of high HIV burden. However, more consequential, the delivery of PrEP to women at high risk of HIV is underdeveloped due to complicated results from clinical trials that assessed PrEP efficacy among women. In order to maximize the impact of PrEP, it is important to understand the different PrEP efficacy results across trials, draw a definitive conclusion about the HIV prevention benefit of PrEP for women, and identify elements from clinical trials and open-label studies that are important to address within programs delivering PrEP to women.

Text of Review

Randomized Clinical Trials of PrEP among Women

Five double-blind, placebo-controlled randomized clinical trials of daily oral TDF-based PrEP that included heterosexual women were conducted [12-16, 67, 95] (Table 1). All trials were carried out in settings with high HIV burden and study subjects received a comprehensive package of HIV prevention services, including frequent HIV testing, risk reduction and adherence counselling, condoms, and treatment for sexually transmitted infections (STI). Participants received intensive adherence counselling to take study drug once per day, and multiple methods were used to measure adherence, including self-report, daily diaries, clinic-based counts of returned pills and bottles, and testing archived blood samples

for tenofovir. Despite similarities in study design and analytic approach, the primary intent-to-treat efficacy results varied substantially across trial populations.

Three of the five studies found that daily oral PrEP reduced the risk of HIV acquisition overall and in subgroup analyses of women. In the Partners PrEP Study, which included 1,785 Kenyan and Ugandan women with a mutually disclosed HIV-infected partner, PrEP efficacy among women was 66% and 71% for the two PrEP medications tested, and PrEP efficacy did not differ substantially between men and women [13]. In further analyses, the protective effect of PrEP was consistent in subgroups of women at high risk for HIV acquisition [95]. PrEP efficacy among women in the TDF2 study in Botswana was 49%, although the small sample size limited statistical precision [15]. Although women comprised only 20% of participants in the Bangkok Tenofovir Study (BTS), PrEP efficacy among this subgroup was 79% [14]. In contrast, two trials among African women, (FEM-PrEP, conducted among 2,120 women from Kenya, Tanzania, and South Africa and VOICE, conducted among 3,019 women from South Africa, Zimbabwe and Uganda), demonstrated no effect of daily oral PrEP on HIV acquisition [12, 16].

Data from all five trials consistently demonstrated that HIV acquisition occurred during periods of low or no adherence to PrEP. Having tenofovir detected in blood samples was associated with ≥85% protection from PrEP [67] and the frequency of tenofovir detection in each overall trial population strongly paralleled the HIV protection observed in each study. In the three trials that demonstrated a protective effect from PrEP, tenofovir was detected in 67-83% of samples from a random subset of participants [13-15], compared to 24-30% in the two trials with null results [12, 16, 96], leading to the conclusion that PrEP protects women from HIV infection when it is used.

Biological Factors Influencing PrEP Efficacy among Women

A number of biological factors have been hypothesized to influence the protective effect of PrEP in women. Foremost among these is the presence of adequate PrEP medication at the time of HIV exposure. Preventing HIV acquisition through sexual contact likely depends on sufficient adherence to achieve tenofovir levels in genital (or rectal) tissues that can prevent viral replication and dissemination.

Men who have sex with men (MSM) and transgender women, for whom rectal exposure carries the greatest HIV risk, appear to benefit from near-complete HIV protection with blood levels reflecting as few as four doses of TDF-based PrEP per week [97]. MSM who used an event-driven, coitally-dependent PrEP regimen achieved high rectal concentrations of tenofovir and reduced HIV acquisition by 86% [98]. The body of evidence to define the level of tenofovir and number of doses required to confer this level to women is limited, particularly studies linking pharmacokinetics to *in vivo* pharmacodynamics. Available data suggest that more consistent dosing is required to achieve sufficient levels of tenofovir in vaginal tissue than rectal tissues [16, 99-101]; however, as demonstrated in the efficacy clinical trials of PrEP, women who were generally adherent to a daily PrEP regimen were strongly protected against HIV.

Additional hypotheses have questioned whether the benefits of PrEP may be compromised in younger women who are more susceptible to HIV because of immature genital mucosa, in women with sexually transmitted infections (STIs), in women who encounter a high viral inoculum (i.e., due to high viral concentrations or acute HIV infection in partners), and due to interactions with hormonal contraceptives [5, 16, 102, 103]. Physiological features, including a higher proportion of exposed cervico-vaginal epithelium tissues, and increased levels of pro-inflammatory cytokines in genital secretions and inflammatory immune cells in cervicovaginal fluid, may put younger women at higher risk of HIV acquisition [104]. On average, HIV-uninfected participants in the Partners PrEP Study, TDF2, and BTS were older than women in FEM-PrEP and VOICE [12, 13, 16]; however, the protective effect of tenofovir-based PrEP was 72-77% in a subgroup analysis of women <30 years old in the Partners PrEP Study [95]. The baseline prevalence of bacterial STIs was lower in the Partners PrEP Study, as compared to VOICE and FEM-PrEP [12, 16, 105], and differences in recurrent and undiagnosed STIs or vaginal washing and drying may have heightened women's susceptibility to HIV [106]. However, PrEP was effective in the Partners PrEP Study, where the protective effect of PrEP was 67-71% in a subgroup analysis of couples diagnosed with an STI in the past three months, and 83% of HIV-uninfected women reported daily vaginal washing [95, 105].

HIV incidence among women in the Partners PrEP Study placebo arm was 2.8 per 100 person years, substantially lower than incidence rates seen in FEM-PrEP (5.0 per 100 person years) and VOICE

(4.2-4.6 per 100 person years) [12, 13, 16]. One proposed explanation for this difference is that women in the Partners PrEP Study were primarily exposed to HIV by chronically infected men, who were potentially less infectious than acutely infected men [106]. While infectivity is a strong predictor of HIV transmission, the majority of infections in generalized HIV epidemics are transmitted from persons with chronic HIV [107, 108], and thus it is likely that the majority of transmissions in FEM-PrEP and VOICE were as well. The overall protective effect of PrEP was 76-78% among all HIV uninfected participants and 72-84% among women whose partner had a viral load ≥50,000 copies/mL in the Partners PrEP Study, providing evidence that the prevention benefit of PrEP was not attenuated with exposure to high HIV viral load [95]. Animal models have demonstrated that the protective effect of TDF-based PrEP does not diminish over time, regardless of the number of challenges, suggesting that there may not be a threshold effect of PrEP when taken with sufficient adherence [109, 110].

The high pregnancy incidence rate among women initiating oral contraceptives during FEM-PrEP initially suggested a potential interaction between oral contraceptives and PrEP [68, 111]. However, low adherence to oral contraceptives, especially among new users, is thought to be the driving factor behind pregnancy incidence and women who adopted oral contraceptives at study enrollment were also less likely to adhere to study drug [96, 112]. TDF-based PrEP does not interact with oral, injectable or implantable contraception to reduce either the effectiveness of contraceptives to prevent unintended pregnancy nor the HIV prevention benefit of PrEP [68, 113]. Indeed, PrEP is one strategy that could mitigate concern regarding the potential increased risk for HIV acquisition among women using progestin-based injectable contraception [114].

Behavioral Factors Influencing PrEP Effectiveness among Women

Although challenging to accurately measure, motivation to prevent HIV acquisition is likely tied to self-perceived risk, which in turn influences adherence to HIV prevention strategies [115]. Despite inclusion criteria based on objective measures of HIV risk and the high observed HIV incidence among placebo arm participants [116], 50% of women enrolled in FEM-PrEP thought they had “no chance” of acquiring HIV in the next 12 weeks and seroconverters described underestimating their risk and rationalizing their risk behavior(s) [16, 115, 117]. Older participants in BTS, VOICE, and the Partners

PrEP Study had higher adherence [12, 118, 119]; younger participants in VOICE and FEM-PrEP were likely less experienced navigating personal risk and this may have influenced their HIV prevention decision-making [5]. In qualitative interviews, VOICE participants acknowledged that their trial participation was motivated by increased HIV risk from male partners with additional sexual partners, however women often had to compromise study drug adherence and keep their trial participation covert to maintain these relationships [120].

Across trials, personal assessment of high HIV risk, coupled with social and clinic-based support, facilitated greater self-efficacy to adhere to daily oral PrEP. HIV uninfected participants in the Partners PrEP Study had known exposure to HIV from their mutually-disclosed HIV infected study partner and both partners received adherence counselling during the trial [117]. PrEP provided a solution to the "discordance dilemma" by simultaneously preventing HIV acquisition and maintaining the partnership, especially prior to ART initiation by the HIV infected partner [121]. Low or no adherence to PrEP in the Partners PrEP Study was associated with no or infrequent sex with a study partner, suggesting that participants modified their PrEP use based on fluctuations in their sexual activity and perceived HIV risk [67, 119]. Participants in the BTS were self-identified injection drug users attending drug treatment centers who had potential for parenteral and sexual exposure and 93% of participants elected to attend daily study visits [118]. Although participants did receive compensation for each study visit, these characteristics also suggest a high motivation for risk reduction.

Despite PrEP being a discrete female-controlled prevention method, community-level stigma related to HIV infection impacted women's adherence to study drug [122, 123]. Women in VOICE described the importance of taking their study drugs secretly in order to preserve their healthy, HIV uninfected image [123]. Women perceived stigma associated with HIV and encountered suspicion from community members about why an HIV uninfected person would take antiretrovirals [123]. Men expressed concerns about possible undisclosed HIV positive status and additional sexual partners when their female partners used PrEP. Some male partners felt threatened by women's participation in research and exercising autonomy to access health care [120, 122, 124]. It was taxing for women to

manage social relationships while participating in the VOICE study; these challenges contributed to women concealing study participation and missing PrEP doses [123, 125].

Features of clinical trials also influenced the behaviors of trial participants. Overall study retention in FEM-PrEP and VOICE was 82-91%, and quality clinical care, education, and modest financial reimbursement in settings with limited opportunity for income generation motivated women to maintain their participation [12-16, 120, 125-127]. However, retrospectively, participants in FEM-PrEP and VOICE expressed ambivalence about research and the importance of adhering to study medication, including reluctance to use investigational drugs with the potential for side effects and unknown levels of HIV protection [12, 120, 127]. Inaccurate self-reported adherence was common in the trials. Participants in FEM-PrEP cited perceived consequences, such as trial termination, negative reactions from study staff, and additional time needed to explain their non-adherence during study visits, as reasons for over-reporting adherence [120, 127]. Some VOICE participants believed that tenofovir testing would rectify inaccurate self-reported adherence, and poor adherence by some women could be overcome by high adherence from others [120].

The HIV Prevention Benefit of PrEP Requires Adherence

The conflicting results across trials regarding the benefit of PrEP for women have challenged the HIV prevention community. However, when analyzed collectively, there is a clear conclusion that daily oral TDF-based PrEP is protective for women, established through subgroup analyses, consistency across studies when adherence is evaluated, and bolstered by analogous data from men. Like any medication, adherence is required for PrEP to be efficacious. Pharmacokinetic studies suggest that consistent adherence is required to achieve sufficient concentrations of tenofovir in vaginal tissues and a substantial proportion of women across studies attained this level of high adherence. The lack of a protective effect observed in FEM-PrEP and VOICE can be attributed to overall low adherence to study medication and is not due to biological features unique to women [128, 129]. While adherence challenges observed across all trials have important implications for PrEP delivery to women, they should not detract from the overall conclusion that PrEP protects women from HIV acquisition when taken with sufficient adherence (Figure 1).

Delivering PrEP to Women

The next steps for PrEP delivery to women include implementation within routine healthcare without the incentives of clinical trials, as well as additional research to identify factors influencing HIV susceptibility and understand the minimum level of adherence needed for women to achieve a sufficient HIV protection benefit from daily oral PrEP.

Integrating Time-Limited PrEP into Existing Reproductive Health Services

Integrating HIV risk assessment and PrEP dispensation into established sexual and reproductive health services that women access routinely, including HIV/STI testing and counselling, antenatal care, and contraceptive counselling, is a natural strategy to maximize the impact of PrEP [5]. Delivery strategies for time-limited PrEP use during periods when a woman's HIV risk is greatest – including new partnerships with men of unknown HIV status, with HIV infected male partners prior to ART initiation, during pregnancy attempts and pregnancy when condom use is reduced - are feasible, safe, and cost-effective [17, 71, 130-135]. Providers can use risk scoring tools to identify women with the highest risk for HIV acquisition using routinely collected clinical and demographic data [136, 137].

Facilitating Adherence in Public Health Settings

Individuals' adherence patterns changed relatively little during the clinical trials: in general, those who initiated PrEP maintained their adherence, especially if they adhered through the end of the first month [12, 67]. These findings underscore the importance of accurately assessing PrEP adherence soon after initiation, and then providing continued positive reinforcement to women who are able to achieve high adherence quickly. Greater public health impact may come from prioritizing this sustained high adherence among individuals who initiate PrEP with high adherence as well as assisting women to assess their risk and match PrEP use with the most vulnerable periods [134]. PrEP delivery to women must be coupled with realistic expectations of and mechanisms to facilitate adequate adherence, including personal risk assessment and social support [5, 138-140]. Community sensitization regarding antiretroviral medications for prevention, not just treatment, of HIV may create a context that is more

receptive to PrEP use. When it is safe for a woman to share her desire for HIV prevention, her invitation to a male partner to participate in decision-making about PrEP may facilitate her high adherence.

Initial data suggest that adherence to and HIV protection from PrEP is higher in open label-studies when the HIV prevention benefit is well understood by users. Among MSM enrolled in the PROUD study, high self-reported adherence to daily oral TDF-based PrEP was substantiated by blood tenofovir levels and provided 86% protection from HIV [141]. Among HIV serodiscordant couples enrolled in the Partners Demonstration Project using PrEP as a "bridge" until the HIV infected partner sustains ART use, tenofovir was detected in 86% of samples tested and contributed to an estimated 96% reduction in HIV [142, 143].

Open-label studies also suggest that adherence to daily dosing may be preferred over intermittent or event-driven dosing, perhaps because it fits into daily routines and does not require anticipating sex [144, 145]. In ADAPT (HPTN 067), an open-label study of oral PrEP dosing frequency among young South African women, adherence was assessed through Wisepill monitoring. Women randomized to a daily dosing schedule had higher adherence overall and 75% of sexual acts covered by PrEP, as compared to 52-56% of sex acts among women randomized to less than daily or intermittent dosing to align with sexual activity [144]. Long-acting formulations of PrEP delivered as injectables or vaginal rings, including multi-purpose technologies that provide dual protection against HIV and unintended pregnancy, are currently being evaluated and may provide alternative strategies to daily oral PrEP in the future [146-149]. Analogous to contraception, for which multiple delivery strategies permit choices to accommodate individual women's needs, multiple delivery mechanisms for PrEP may allow more women to achieve HIV protection [150].

Conclusion

Tenofovir-based oral PrEP is an effective HIV prevention strategy for heterosexual women. Significant public health impact from PrEP will require delivery strategies that integrate PrEP into existing health services and address the individual, community, and structural level factors that influence adherence. More than thirty years into the HIV epidemic, oral PrEP is the first intervention that women can control themselves and it offers highly efficacious prevention against HIV.

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None.

Conflicts of interest

None.

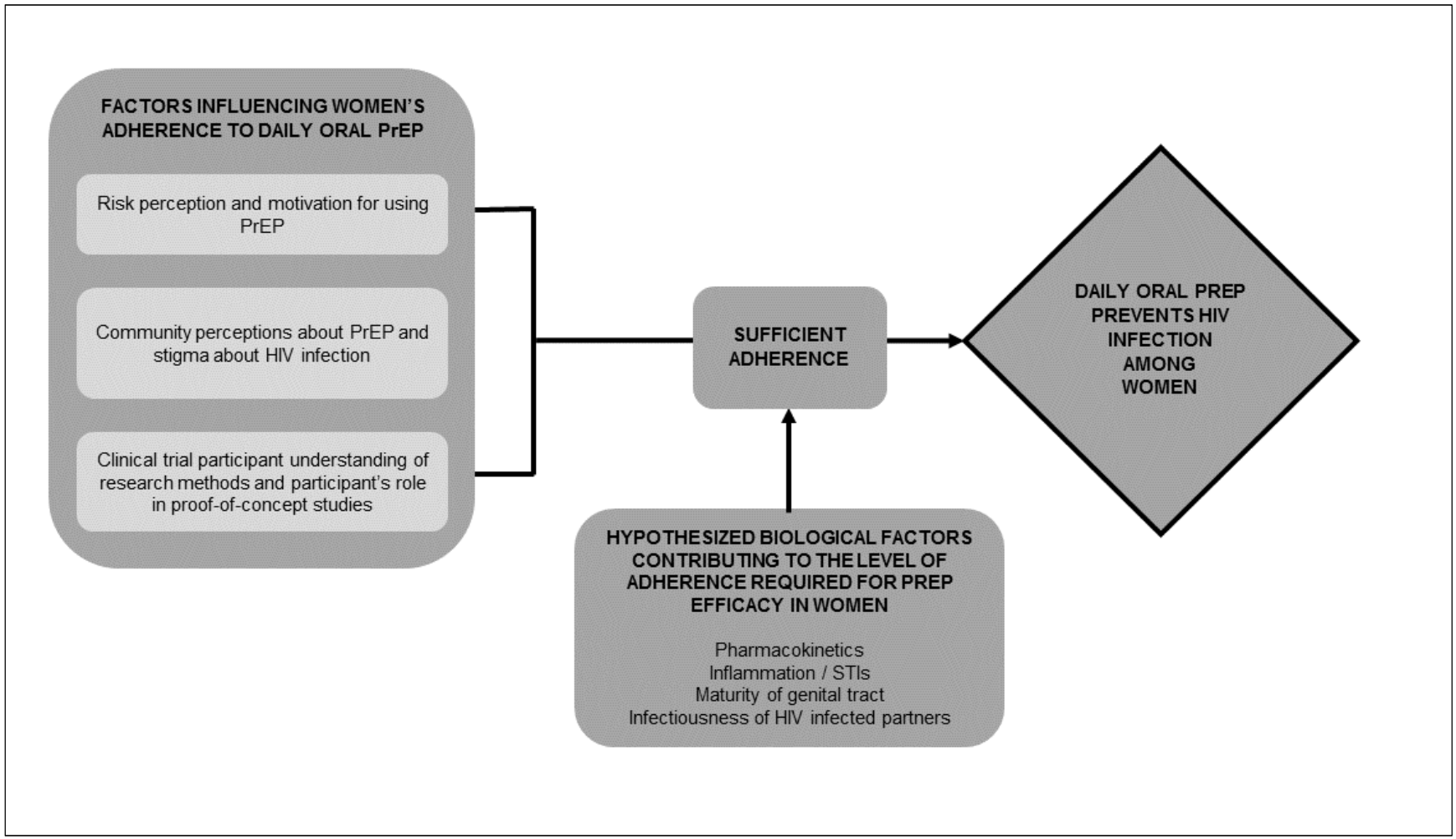
Key Points

- Clinical trial data demonstrate that daily tenofovir-based oral pre-exposure prophylaxis (PrEP) prevents HIV acquisition among women when taken with sufficient adherence.
- Pharmacokinetic studies provide evidence that daily dosing of tenofovir-based oral PrEP reaches concentrations in vaginal tissues that are consistent with levels needed for HIV prevention.
- Evidence from clinical trials and emerging data from open-label studies demonstrate that women who are at risk of HIV and motivated to use PrEP can adhere sufficiently to the daily regimen and be protected against HIV.
- Innovative strategies to motivate women at risk to use daily PrEP and scalable adherence support strategies need to be identified and integrated into delivery models.

Table 7: Double-Blind Placebo-Controlled Randomized Trials that Included HIV Uninfected Heterosexual Women to Assess the Efficacy of Daily Oral Tenofovir Disoproxil Fumarate (TDF)-Based Pre-Exposure Prophylaxis (PrEP) for HIV Prevention							
Study Characteristics				**Benefit of PrEP (95% CI)**			
Name	**Study Population**	**Sample Size**	**Oral PrEP Agent**	**Plasma TDF in a Random Sample of Participants**	**Overall Efficacy**	**Female Subgroup Efficacy**	**Additional Analyses among Women**
Partners PrEP Study Baeten et al. [13, 67, 95]	Heterosexual HIV-1 uninfected persons in HIV-1 serodiscordant relationships: Kenya, Uganda	4,747 serodiscordant couples (including 1,785 in which the HIV uninfected partner was female)	TDF-FTC	81%	75% (55, 87%)	66% (28, 84%)	Tenofovir > 40 ng / mL: 94% (-17, 100%) Age < 30 years: 72% (25, 90%) Partner viral load > 50,000 copies/mL: 72% (13, 91%)
			TDF	83%	67% (44, 81%)	71% (37, 87%)	Tenofovir > 40 ng / mL: 85% (-90, 99%) Age < 30 years: 77% (29, 92%) Partner viral load > 50,000 copies/mL: 84% (29, 96%)
TDF2 Thigpen et al.	Heterosexual men and women: Botswana	1,219 (557 women)	TDF-FTC	79%	62% (22, 83%)	49% (-22, 81%)	With censoring after self-reported discontinuation of study medication: 75% (24, 94%)
Bangkok Tenofovir Study Choopanya et al.	Male and female injection drug users: Thailand	2,413 (489 women)	TDF	67%	49% (10, 72%)	79% (17, 97%)	
FEM-PrEP Van Damme et al.	Heterosexual women: Kenya, Tanzania, and South Africa	2,120 women	TDF-FTC	24%	6% (-52, 41%)	NA	

VOICE Marrazzo et al.	Heterosexual women: South Africa, Uganda, Zimbabwe	3,019 women (an additional 2,010 women were assigned to tenofovir gel)	TDF-FTC	29%	-4% (-49, 27%)	NA	
			TDF	30%	-49% (-129, 3%)	NA	

Figure 3: Schematic depicting the totality of evidence for tenofovir-based oral pre-exposure prophylaxis (PrEP) to prevent HIV among women



CHAPTER 4: Fertility Desires and Preferences for Safer Conception Strategies among People Receiving Care for HIV at a Publicly-Funded Clinic in Seattle, WA

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Fertility Desires and Preferences for Safer Conception Strategies among People Receiving Care for HIV at a Publicly-Funded Clinic in Seattle, WA

Kerry A. Thomson, MPH[1]
Shireesha Dhanireddy, MD[2]
Michele Andrasik, PhD, MS[3]
Kerry Hancuch, MPH[1]
Lindsay Legg, LPN[4]
Jacob Keane-Candib, BA[4]
Renee Heffron, PhD, MPH[1]

Author Affiliations: [1]University of Washington Department of Epidemiology, [2]University of Washington Department of Medicine, Harborview Hospital, [3]University of Washington Fred Hutchinson Cancer Research Center, [4]University of Washington Department of Global Health, Harborview Hospital

Corresponding author:

Renee Heffron
325 Ninth Avenue Box 359927, Seattle, WA, USA 98104
Phone: +1 206-520-3817, Fax: + 1 206-520-3831

Email: rheffron@uw.edu

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Abstract

Understanding fertility desires and preferences for HIV prevention among individuals living with HIV, including the potential use of pre-exposure prophylaxis (PrEP) by HIV uninfected partners, can inform the delivery of safer conception counselling to reduce the risk of HIV transmission during pregnancy attempts. Men and women, predominantly heterosexual, engaged in HIV care in Seattle, WA, self-administered a questionnaire and we abstracted antiretroviral therapy (ART) status and HIV viral levels from medical records. We summarized participants' sexual behavior, fertility desires, and preferences for safer conception strategies and used log-binomial regression to identify demographic, sexual, and behavioral factors associated with perceived acceptability of PrEP for HIV uninfected partners during pregnancy attempts. 52% of the 150 participants were female and the mean age was 48 years (range 23-74). 94.7% of participants were using ART and 79.3% had HIV viral load < 40 copies/mL. 22.2% of men and 34.6% of women reported that a healthcare provider had initiated discussion about fertility desires. 28.7% of participants were reproductive-age and desired children. Among sexually active reproductive-age participants with fertility desires, 56.3% reported inconsistent condom use and 62.5% did not report using effective birth control. 74.4% of reproductive age participants with fertility desires perceived that PrEP would be acceptable to an HIV uninfected partner and there were no significant predictors of PrEP acceptability. Nearly one third of reproductive-aged individuals living with HIV expressed fertility desires, highlighting a need for safer conception counselling in this setting. PrEP and ART were favored safer conception strategies.

Introduction

Effective management of HIV with antiretroviral therapy has enabled people living with HIV to achieve full life expectancy, including satisfying desires for pregnancy and family [151-158]. The preconception period, when couples intentionally forgo condoms to achieve pregnancy, can be accompanied by increased HIV transmission risk [159], especially when viremia is not fully suppressed in the partner living with HIV. The majority of people living with HIV in King County, WA are of reproductive age and an estimated 25% of those living with HIV who identify as heterosexual have unsuppressed HIV viremia [4], suggesting that there may be prevention gaps for HIV affected individuals and couples who want to attempt pregnancy.

"Safer conception" is a risk reduction approach where individuals affected by HIV use one or more strategy to reduce the risk of HIV transmission and optimize fertility during pregnancy attempts. Antiretroviral treatment (ART) has tremendous clinical and prevention benefits [160, 161] and can form the cornerstone of safer conception as it permits conception through sexual intercourse (i.e. "natural" conception) and is safe to use during pregnancy attempts [19, 20, 159, 162, 163]. Additional safer conception strategies that can be used alone or in combination with ART include pre-exposure prophylaxis (PrEP) used by HIV uninfected people, condomless sex timed to days with peak fertility, treatment for sexually transmitted infections, vaginal self-insemination, and medically assisted reproduction (sperm washing in conjunction with intrauterine insemination (IUI), *in vitro* fertilization, or intra-cytoplasmic sperm injection (ICSI)) [163]. Since ART initiation is sometimes delayed and adherence to daily ART regimens can be challenging, these conjunctive strategies are important options for couples who desire enhanced HIV prevention during the periconception and pregnancy periods [159, 162].

Demand for information and access to safer conception strategies is growing among individuals affected by HIV and providers frequently lack experience or knowledge about these services [164-168]. The purpose of the current study was to describe fertility desires and preferences for safer conception strategies among individuals living with HIV in Seattle, WA and to consider whether PrEP would be an acceptable strategy to offer to their uninfected partners.

Methods

Data collection

We conducted a cross-sectional study at the largest HIV clinic in Seattle, WA (Madison Clinic, University of Washington Harborview Medical Center). As a publicly funded institution, the Madison Clinic provides comprehensive care for all individuals, regardless of their insurance status or ability to pay. PrEP for HIV uninfected individuals has been available at the clinic since October 2014.

In 1992 the Madison Clinic established a research referral registry that includes patients who consent to be contacted by clinic-affiliated researchers for recruitment into research. For the current study, English-speaking, HIV-infected patients aged ≥21 who completed at least one HIV care visit in the previous 12 months and did not self-identify in the registry as men who have sex with men (MSM) were eligible to participate. The clinic generated a preliminary list of potentially eligible patients from the research registry and a research nurse contacted patients via phone to confirm eligibility. Demographic information was available for all potentially eligible patients included on this initial list, allowing for a comparison between patients who enrolled in the current study and those who did not. Three attempts were made to contact each potentially eligible patient, screen for eligibility criteria, and schedule an interview time. For patients who were unreachable by phone, the research nurse attempted to recruit them in person on the day of an already scheduled clinic visit. Eligible participants were given basic information about the study, and were scheduled for study visits if they expressed interest in participating.

Between July 2015 and June 2016, participants self-administered a computer-based questionnaire hosted through REDCap (Research Electronic Data Capture), a secure web-based application for data capture (University of Washington Institute of Translational Health Sciences) in a confidential clinic room. The questionnaire consisted of 70 items to assess: 1) demographics; 2) relationship and partner characteristics; 3) sexual behavior; 4) HIV diagnosis, ART use and adherence; 5) fertility history and desires; and 6) awareness of, willingness to use, and barriers to using safer conception strategies. Participants were asked about their preferences regarding six specific safer conceptions strategies: antiretrovirals (ART and PrEP), medically assisted reproduction, vaginal self-insemination, timed condomless sex, and treatment for sexually transmitted infections. An information sheet that explained these safer conception strategies in layperson language was available to participants while completing the questionnaire. Participants were asked to report on their perceived acceptability of

PrEP as a safer conception strategy to either a current or future HIV negative partner. Participants rank-ordered their top three preferred strategies to use for safer conception in response to a scenario in which they were attempting pregnancy with an HIV uninfected partner and all potential barriers to these strategies (e.g. knowledge, cost, access) were removed. Following the survey, medical record abstraction was done to capture participants' most recent HIV viral load and CD4 count results and to verify self-reported ART use.

Protocols for the current study and the clinic registry were approved by the Human Subjects Division at the University of Washington. All participants provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization to access their medical records.

Statistical Methods

We used descriptive methods to compare demographic characteristics between eligible patients who did and did not enroll in the current study, and then summarized demographics, clinical characteristics, sexual behavior, and fertility desires among those who enrolled. Further analyses were restricted to a subset of participants who were categorized as reproductive age and expressed the desire to have at least one child in the future. In this subset, we used descriptive methods to describe knowledge of, willingness to use, and preferences for safer conception strategies and log binomial regression to determine factors associated with perceived acceptability of PrEP as a safer conception strategy to HIV uninfected partners. We adjusted the multivariable model for HIV serodiscordant relationship status (yes = currently in a relationship with a known HIV uninfected partner, no = not currently in a relationship or in a relationship with a partner of unknown or HIV infected status) based on *a priori* decisions. In addition, we included any factor that was statistically significant in univariate analyses ($p \leq 0.05$). Men of any age and women less than 45 years were categorized as reproductive age [169]. Effective contraception included oral contraceptive pills, injectable, rings, implant, IUD, or permanent methods. Undetectable HIV viral load was defined as <40 copies/ml. SAS 9.4 (Cary, North Carolina) was used for all analyses.

Results

A total of 481 patients were identified from the research registry as eligible, of which 150 (31.2%) enrolled in the study, 259 (53.8%) could not be contacted to confirm eligibility, and 72 refused to

participate (15.0%). The most common reasons for refusal were disinterest in the study (52.8%) and the time required to participate (19.4%). Based on registry data, a higher proportion of participants who enrolled in the study were born in the USA, but otherwise there were no differences between those that enrolled and those that did not enroll with regard to sex, age, race, or ethnicity.

Participant characteristics

Approximately half (52%) of enrolled participants were female and the mean age for men and women was 49.2 (range 25-74) and 47.7 (range 23-68), respectively (Table 8). One third of all women (35.9%) were categorized as being within reproductive age. A quarter of participants did not graduate from high school and 64.7% reported having difficulty paying their monthly bills The mean number of years since HIV diagnosis was 14 (range 0-31), almost all participants (94.7%) were on ART, and 79.3% had undetectable HIV viral load. About half (42%) of all participants were in a committed heterosexual relationship and of these, 71.4% were in an HIV serodiscordant relationship. Less than half of participants (43.6% of women and 36.1% of men) reported sexual activity in the 30 days prior to completing the survey. Sexually active participants reported a mean of 8.5 sex acts in the past 30 days (range 1-25), 53.3% reported inconsistent condom use during sex, and 28.3% reported using effective contraception.

Fertility history and desires

Twenty nine percent of all participants and 34.9% of reproductive age participants with fertility desires reported that a healthcare provider (HIV, gynecologist, or primary care) had ever initiated a conversation about fertility desires (Table 8). More than half of participants (66.0%) reported having one or more biological child. Fourteen percent of all participants, and 25.6% of participants of reproductive age with fertility desires, reported a previous pregnancy attempt with an HIV uninfected partner and 51.7% of all female participants with a history of pregnancy reported that their most recent pregnancy was mistimed or unwanted. Forty percent of reproductive age participants with fertility desires perceived that they were unable to have children; reasons included the perception that HIV or ART affect fertility (50.0%), age-related factors (44.4%), and history of unprotected sex that did not result in pregnancy (27.8%).Almost one third of participants (28.7%) were of reproductive age and had a desire to have one or more biological child at some point in the future (Figure 4).

Awareness of and preferences for safer conception strategies

Participants of reproductive age with fertility desires (n=43) were generally aware of and willing to use safer conception strategies (Table 9). ART was the most commonly recognized strategy (79.1%), followed by medically assisted reproductive health technologies (55.8%), PrEP (48.8%), and timed condomless sex (44.2%). Willingness followed a similar pattern with high willingness for ART (90.1%), followed by PrEP (74.4%), medically assisted reproductive health technologies (67.4%), and timed condomless sex (60.5%). When responding to a hypothetical scenario where all barriers to accessing safer conception strategies were removed and participants could rank their top three choices, participants favored ART (76.7%), PrEP (60.4%), and medically assisted reproductive health technologies (44.1%).

Acceptability of PrEP for safer conception

Univariate regression analysis did not identify any demographic, fertility history, sexual behavior, or HIV clinical characteristics that were significantly associated with perceived acceptability of PrEP (Table 10). The majority of reproductive age participants with fertility desires (62.8%) reported at least one barrier to PrEP utilization by a current or future HIV uninfected partner including not having heard of PrEP (20.9%), perceived side-effects (18.6%), concerns about the influence of PrEP on pregnancy or birth outcomes (14.0%), and cost (14.0%). Participants who anticipated one or more barrier to PrEP use were 33% less likely to perceive that a current or future partner would be willing to use PrEP during pregnancy attempts (prevalence ratio (PR): 0.67, 95% CI: 0.49, 0.92, p=0.01), although this association was no longer significant after adjusting for current status in an HIV serodiscordant relationship (aPR: 0.75, 95% CI: 0.54, 1.06, p=0.11).

Discussion

Our study describes the fertility desires and preferences for safer conception strategies among a racially diverse and economically vulnerable population of men and women engaged in HIV care at a publicly funded clinic in Seattle, WA. While the majority of participants were older and already have children, 28.7% of reproductive age participants reported that they desire one or more child in the future. Among this subset of reproductive age men and women with fertility desires, HIV serodiscordant partnerships were common, inconsistent condom use was high, and use of effective contraception was

low. Only a third of patients reported that a healthcare provider had initiated conversation about fertility desires, suggesting that there are missed opportunities for providers to discuss pregnancy planning and to recommend prevention interventions to their patients.

The ability to decide the number, timing, and spacing of children is recognized as a basic human right [170]. For individuals and couples affected by HIV, intentionally planning or preventing pregnancy is a critical step in reducing the risk of sexual and perinatal HIV transmission. Fertility desires may fluctuate over time based on a variety of factors, such as age, partnership status, health status, and financial security. Frequent assessment of sexual partnerships and fertility desires is an opportunity for medical providers to assist patients in planning and achieving their fertility goals, whether that is effective contraception or intended pregnancy, preconception health, and/or safer conception strategies. A recent study among women living with HIV in Florida found that approval from a healthcare provider was the second most important factor influencing a woman's decisions around childbearing [171]. In our study, only a third of patients reported that a healthcare provider had initiated a conversation with them about fertility desires. This finding is similar to a cross-sectional assessment among women receiving HIV care at two urban clinics in the US; 40% of 181 women reported a desire for a child, however 23% of these women were identified as having an unmet need for safer conception counselling [172]. Almost half of the reproductive age participants with fertility desires in the current study reported that they did not perceive themselves as fertile, and of these the majority perceived that their HIV status and/or taking ART affected their fertility. In many cases, participants were willing to use safer conception strategies but lacked awareness of them. These results highlight important knowledge gaps that can be addressed by primary care, gynecology, and HIV providers.

Among participants of reproductive age with fertility desires, willingness to use safer conception strategies was highest for ART, PrEP, and medically assisted reproduction, and these three strategies, respectively, were the most preferred strategies when participants were asked to select their top three safer conception strategies. Medically assisted reproduction, as sperm washing combined with IUI, ICSI, or IVF, require specialty care, is limited to one fertilization attempt per ovulatory cycle, and may be accompanied by high out of pocket expenses [173, 174]. The majority of patients at the Madison Clinic

are covered by Medicaid and a high proportion of reproductive age participants with fertility desires reported that they have difficulty paying their monthly bills, suggesting that these patients may need alternative safer conception strategies that that are less expensive than medically assisted reproduction.

Almost all participants in our study population were on ART, the majority of whom had undetectable HIV viral load and high self-reported adherence to ART. A recent mathematical model estimated that PrEP confers very little additive benefit (0.1% -0.2%) for HIV prevention when used in addition to suppressive ART [175]. However, this model was based on data from mutually disclosed HIV serodiscordant couples and assumed consistent adherence to ART with condomless sex restricted to peak fertility days [162]. ART use alone may be insufficient as a safer conception strategy, including instances when the person living with HIV is unable to achieve high adherence to ART and HIV viral suppression or in circumstances when the HIV status of a sexual partner is unknown [162]. Multiple clinical guidelines, including those from World Health Organization [75], the American College of Obstetrics and Gynecologists [77], and the US Panel on the Treatment of HIV Infected Pregnant Women and Prevention of Perinatal Transmission [19], recommend PrEP as a safer conception strategy for individuals at high risk of HIV, and previous studies have demonstrated that couples affected by HIV welcome the opportunity to augment ART use with PrEP during pregnancy attempts.[78, 132, 155, 176-178] Reported experience with PrEP was low among participants in our study with an HIV uninfected partner. Awareness of PrEP as a safer conception strategy was moderate among reproductive age participants with fertility desires and many identified potential barriers to HIV uninfected partners using PrEP during pregnancy attempts. These results highlight the need and opportunity to increase knowledge of and address barriers to PrEP utilization among populations that may have HIV uninfected sexual partners.

To our knowledge, this is the first assessment of fertility desires among men and women living with HIV in the Pacific Northwest region and we captured a sample of both men and women representative of the clinic population. Our study was limited to people living with HIV with sufficient literacy to complete a computer-based interview in English. Self-administered interviews may have reduced social desirability bias in the reporting of sensitive information and we were able to collect and

verify clinical HIV data through medical chart review. Recruitment attempts were made via phone and in-person at clinic visits. Potentially eligible participants who could not be contacted are likely disengaged from care. Our final study population reflects active patients able to engage in continued safer conception counseling. Reassuringly, we did not find any demographic differences between individuals who did and did not enroll in the current study. Our study population included a small number of participants who self-reported sexual activity with same-sex partners for whom conception may not be achievable without medically assisted reproductive health technologies, gamete donation, or adoption. Future studies could target greater numbers of people living with HIV in same-sex partnerships to assess their fertility desires, preferences, and experiences with these methods to achieve their family goals. Our results describe the fertility desires of an older population engaged in HIV care, however women may still be fecund beyond the standard categorization of reproductive age and men can continue reproducing into advanced age. Delayed childbearing is becoming more common in the US; the mean age of a woman's first birth has been steadily rising among the general population and from 2000 to 2014 and the proportion of first births to women age 35 or older increased by 23% [179]. Future studies should seek to include populations that may have different fertility desires and preferences for safe conception strategies than what we have captured here, including younger individuals, non-English speakers, who likely include foreign-born individuals living in this area of the US, members of same-sex couples, and the HIV uninfected members of HIV serodiscordant couples.

Many of the men and women living with HIV in our study desire children and are interested in receiving education on safer conception strategies, however conversations on fertility desires between patients and HIV providers appear to be limited. Routinely engaging patients living with HIV in discussions about fertility desires and sexual behaviors is an opportunity for providers to address patient needs for preventing or planning pregnancy and engage them in discussion about their preferred safer conception strategies to minimize the risk of onward HIV transmission during pregnancy attempts.

Gelocation: Seattle, Washington, USA

Acknowledgments: We thank the participants for their time and contributions to this study, as well as the efforts of the study team who facilitated the interview process.

Table 8: Participant Characteristics, N=150, frequency (%) or mean (range)			
	All Men 72 (48.0)	All Women 78 (52.0)	Reproductive Age* and Desire ≥ 1 Child 43 (28.7)
Demographics			
Race / Ethnicity			
American Indian or Alaska Native	5 (6.9)	10 (12.8)	2 (4.7)
Asian	1 (1.4)	5 (6.4)	2 (4.7)
Black or African American	26 (36.1)	33 (42.3)	17 (39.5)
Hispanic or Latino/a	9 (12.5)	4 (5.1)	4 (9.3)
Native Hawaiian or other Pacific Islander	1 (1.3)	2 (2.6)	2 (4.7)
White / Caucasian	36 (50.0)	32 (41.0)	20 (46.5)
Born in USA	63 (87.5)	69 (88.5)	35 (81.4)
Highest level of education			
Less than high school	13 (18.1)	22 (28.2)	8 (18.6)
High school graduate / GED	23 (31.9)	19 (24.3)	11 (25.6)
Post-secondary schooling	36 (50.0)	37 (47.4)	24 (55.8)
Have difficulty paying monthly bills and expenses	44 (61.1)	53 (68.0)	34 (79.1)
Clinical Characteristics			
Years since HIV diagnosis	12.9 (0-31)	15.0 (1-30)	10.6 (0-31)
CD4 Count	517.6 (48-1,774)	583.6 (17-1,604)	489.2 (102-1,361)
Undetectable HIV RNA viral load (< 40 copies / ml)	61 (85.9)	58 (74.4)	35 (83.3)
HIV viral load for those with virus ≥ 40 Log_{10} copies / ml	3.59 (2.25-4.21)	2.19 (1.90-3.50)	2.94 (1.97-3.64)
Currently on antiretroviral therapy (ART)	71 (98.6)	71 (91.0)	39 (90.7)
- Self-reported adherence to ART			
All or most of the time	66 (94.3)	70 (98.6)	38 (97.4)
About half of the time	3 (4.3)	1 (1.4)	1 (2.6)
Never	1 (1.4)	--	--
Healthcare provider has initiated discussion on fertility desires ǂ	16 (22.2)	27 (34.6)	15 (34.9)
Partnerships and Sexual Activity			
Heterosexual or bisexual sexual partnerships	63 (87.5)	72 (92.3)	37 (86.1)
In committed heterosexual relationship	26 (36.1)	37 (47.4)	17 (39.5)
- Respondent has disclosed HIV status to partner	25 (96.2)	34 (91.9)	17 (100.0)
- Partner HIV Uninfected	18 (69.2)	27 (73.0)	12 (70.1)
- Partner has used HIV pre-exposure prophylaxis	2 (11.1)	3 (11.1)	3 (25.0)
- Discussed fertility desires with current partner	22 (84.6)	29 (78.4)	17 (100.0)
Sexually active past 30 days†	26 (36.1)	34 (43.6)	16 (37.2)
- Number of sexual partners in past 30 days	1.1 (1-3)	1.1 (1-3)	1 (1-1)
- Number of sex acts in past 30 days	8.1 (1-25)	8.8 (1-25)	12.4 (1-25)
- Number of condomless sex acts past 30 days	4.3 (0-25)	6.0 (0-25)	9.2 (0-25)
- Inconsistent condom use past 30 days	10 (38.5)	22 (64.7)	9 (56.3)

- Currently using effective contraception**	4 (15.4)	13 (38.2)	6 (37.5)
- Perceived risk of HIV transmission is 'moderate' or 'high'	6 (23.1)	2 (5.9)	2 (12.5)

*Reproductive age included men of any age and women < 45 years of age
ǂ Healthcare provider includes HIV specialist, gynecologist, or primary care provider
†Sexual activity defined as penile-vaginal sex
** Effective contraception includes pills, IUD, implants, ring, injectable, female hysterectomy / tubal, male vasectomy. No participant of reproductive age with fertility desires reported female hysterectomy / tubal or male vasectomy.

Table 9: Awareness, willingness, and preferences for safer conception strategies when attempting pregnancy within an HIV serodiscordant relationship as reported by HIV-infected participants of reproductive age* with any fertility desire, N=43, frequency, (%)

	Antiretroviral Therapy (ART)	Pre-Exposure Prophylaxis (PrEP)	Medically Assisted Reproduction**	Timed Condomless Sex	Treatment of STIs	Vaginal Self-Insemination
Aware of strategy for safer conception	34 (79.1)	21 (48.8)	24 (55.8)	19 (44.2)	9 (20.9)	11 (25.6)
Willing to use strategy for safer conception	39 (90.1)	32 (74.4)	29 (67.4)	26 (60.5)	13 (30.2)	13 (30.2)
Strategy ranked in top 3 preferences for safer conception	33 (76.7)	26 (60.4)	19 (44.1)	13 (30.2)	3 (7.0)	8 (18.6)

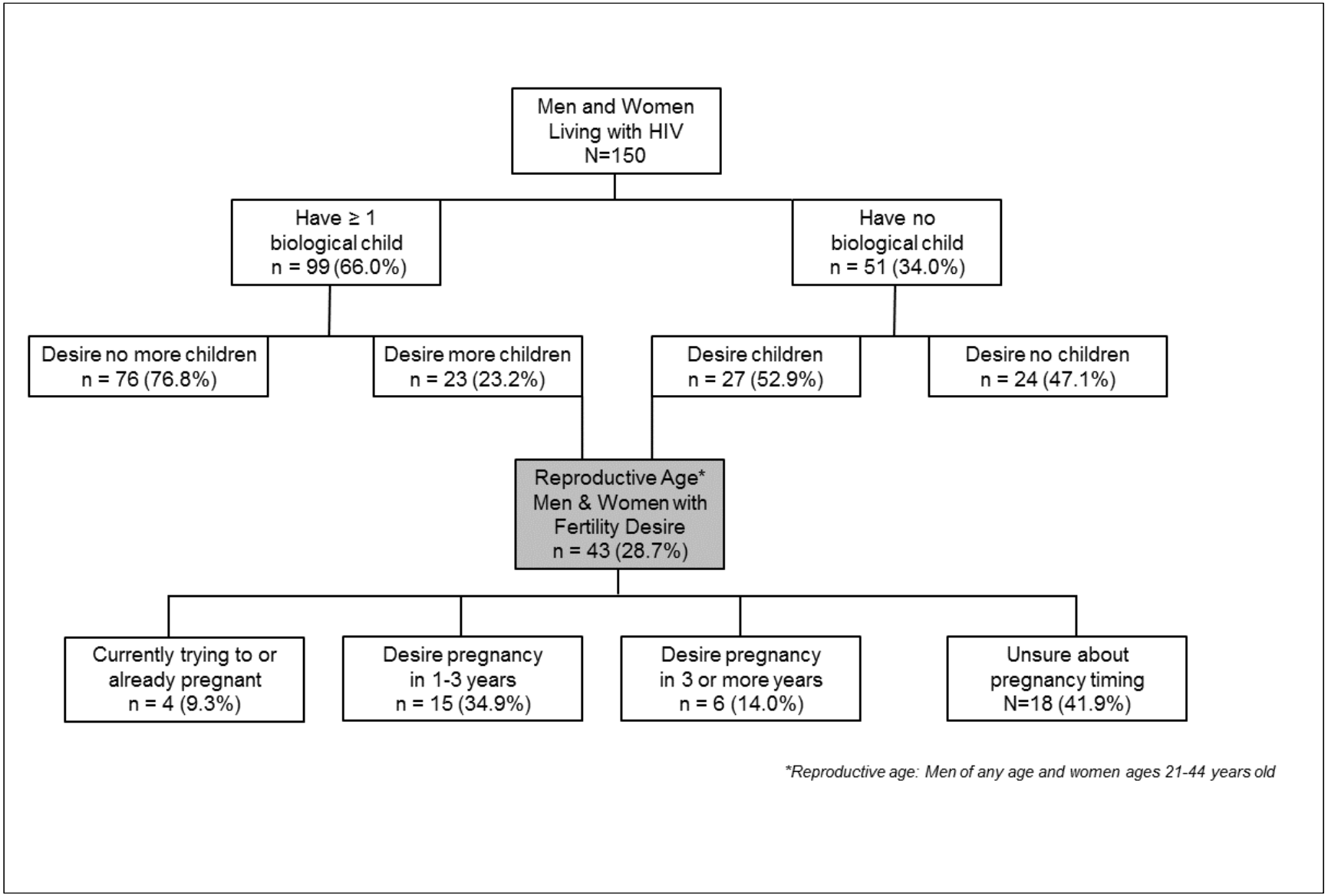
*Reproductive age included male participants of any age and female participants < 45 years of age
** Medically assisted reproduction defined as sperm washing in conjunction with intrauterine insemination (IUI), in vitro fertilization, or intra-cytoplasmic sperm injection (ICSI)

Table 10: Correlates of perceived willingness to for a HIV uninfected partner to use pre-exposure prophylaxis (PrEP) as a safer conception strategy as reported by reproductive age* persons living with HIV and want to have a child in the future, N=43, frequency, (%)				
	Yes N=32 (74.4)	**No or Not Sure N = 11 (26.2)**	**Prevalence Ratio (95% CI)**	**P-value**
Demographics				
Age				
21-29	4 (12.9)	3 (27.3)	0.74 (0.37, 1.50)	0.41
30-39	14 (45.2)	4 (36.4)	1.01 (0.71, 1.46)	0.93
40 and older (reference group)	13 (41.9)	4 (36.4)	--	--
Female (versus male)	12 (37.5)	2 (18.2)	1.25 (0.90, 1.72)	0.19
Born in USA (versus foreign born)	26 (81.3)	9 (81.8)	0.99 (0.63, 1.55)	0.97
Has education higher than high school (versus high school graduate or less)	19 (59.4)	5 (45.5)	1.16 (0.80, 1.67)	0.45
Has difficulty paying monthly bills and expenses	25 (78.1)	9 (81.8)	0.95 (0.63, 1.42)	0.78
Fertility History and Intentions				
Has at least one biological child (versus no biological children)	13 (40.6)	4 (36.4)	1.05 (0.74, 1.49)	0.80
Using effective birth control (versus infective or no birth control)	6 (18.8)	2 (18.2)	1.01 (0.65, 1.58)	0.97
Fertility intent is within 3 years (versus fertility intent greater than three years or unsure)	19 (59.4)	5 (45.5)	1.16 (0.81, 1.67)	0.44
Has discussed fertility desires with healthcare provider	12 (37.5)	3 (27.3)	1.12 (0.79, 1.58)	0.52
Has had at least one previous pregnancy attempt with an HIV uninfected partner	7 (21.9)	4 (36.4)	0.81 (0.50, 1.32)	0.41
Sexual Behavior and HIV Transmission Risk				
Sexually active past 30 days	13 (40.6)	3 (27.7)	1.15 (0.82, 1.62)	0.41
Any condomless sex in past 30 days	7 (21.9)	2 (18.2)	1.06 (0.71, 1.58)	0.79
Perceive high or moderate HIV transmission risk (versus low, no, or unclear risk)	5 (16.7)	5 (50.0)	0.60 (0.32, 1.14)	0.12
Currently in known HIV serodiscordant relationship (versus. no relationship or partner HIV status is infected or unknown)	10 (31.3)	2 (18.2)	1.17 (0.84, 1.65)	0.35

HIV Clinical Characteristics				
On ART (self-report)	29 (90.6)	10 (90.9)	1.01 (0.56, 1.83)	0.98
Self-reported ART adherence is "all the time" (versus adherence less than all of the time)	24 (77.4)	8 (72.7)	0.87 (0.58, 1.32)	0.52
Undetectable HIV viral load (<40 copies/ml)	24 (75.0)	8 (72.7)	1.07 (0.68, 1.68)	0.77
CD4 count ≥ 500 vs. ≤ 499 cells/mm^3	15 (48.4)	4 (36.4)	1.13 (0.79, 1.62)	0.49
Barriers to PrEP Use**				
Reported at least one barrier to PrEP use	17 (53.1)	10 (90.9)	0.67 (0.49, 0.92)	0.01

*Reproductive age included male participants of any age and female participants < 45 years of age
**Options for perceived barriers included: No prior knowledge of PrEP, not knowing where to obtain PrEP, taking a daily pill, side effects for HIV-1 uninfected partner, harmful effects on an infant, concerns about drug resistance, and cost.

Figure 4: Fertility desires and pregnancy timing among all enrolled participants, N=150, frequency, (%)



CHAPTER 5: Conclusion

The work included in this dissertation contributes a better understanding of increased female HIV-1 risk during pregnancy and postpartum, makes a conclusive case that PrEP is efficacious for women, and demonstrates that HIV-1 infected individuals with fertility desires welcome antiretroviral-based safer conception strategies. Combined, these studies make a compelling case for enhanced HIV-1 prevention, especially PrEP, during periods of increased HIV-1 risk. Key opportunities for effective HIV-1 prevention can leverage existing health services before, during, and immediately after pregnancy, to provide HIV-1 testing and initiation of ART among women and their male partners who are diagnosed with HIV-1 and delivery of PrEP for persons testing HIV-1 negative. Increased delivery of these strategies, including strengthening integration of HIV-1 prevention within routine antenatal and postnatal care in settings with high HIV-1 prevalence and provision of safer conception counselling for HIV-1 serodiscordant couples attempting pregnancy, is urgently needed to reduce HIV-1 acquisition.

INTERPRETATIONS AND FUTURE DIRECTIONS FOR INTEGRATION OF HIV-1 PREVENTION AND REPRODUCTIVE HEALTH

Increased risk of female HIV-1 acquisition during time periods related to pregnancy

Our results in *Chapter 2* provide additional and robust evidence that the risk of female HIV-1 acquisition is higher during pregnancy, including the postpartum period, relative to non-pregnant time periods. The risk of HIV-1 acquisition was nearly 3-times higher during late pregnancy (aRR 2.82, 95% CI: 1.29-6.15, p=0.01) and 4-times higher in the postpartum period (aRR 3.97, 95% CI: 1.50, 10.51, p=0.01). Our finding that female HIV-1 risk is nearly four-times higher during the postpartum period is particularly novel. These are the strongest and most robust per coital act risk estimates available to date that are specific to pregnancy-related time periods. We used very high quality data from multiple clinical trials and an analytical approach with several methodological strengths that contribute to our confidence in the results. By estimating the risk of female HIV-1 acquisition per coital act, we were able to address the hypothesis that decreased sexual frequency during the pregnancy and postpartum period obscures increased biological risk in HIV-1 acquisition from pregnancy itself. We confirmed that sexual frequency is lower during pregnancy and postpartum, leading to an increased risk of HIV-1 acquisition per coital act,

results that strongly suggest that biological changes unique to these periods, and not changes in sexual behavior, explain the increase in female HIV-1 incidence during pregnancy and postpartum observed in our analysis and previous study populations.

Our study did not directly assess biological changes that accompany the pregnancy and postpartum periods. While future studies to confirm specific biological mechanisms that increase female HIV-1 susceptibility during these time periods would be useful, the body of observational data, including what we have contributed in *Chapter 2* of this dissertation, is sufficient to justify the need for enhanced HIV-1 prevention during time periods when women, and subsequently their infants, may be at increased risk of HIV-1 acquisition.

PrEP as an HIV-1 prevention strategy for pregnant and postpartum women

When primary prevention of female HIV-1 is achieved, both maternal and infant HIV-1 infection is averted, a tremendous benefit to women, their current pregnancy, and future children. HIV-1 prevention strategies available to women at risk of sexual HIV-1 transmission include abstinence from sexual activity, female and male condoms, and ART use or voluntary male medical circumcision by their partners; however, all of these strategies depend on cooperation from and/or HIV-1 testing by their male partner. *Chapter 3* has addressed the controversy that beset the HIV-1 prevention community in the aftermath of divergent results from the PrEP efficacy trials that enrolled heterosexual women. While cursory and narrow review of the primary results from these five studies provoked concerns about whether daily oral tenofovir-based PrEP is efficacious for women, our comprehensive review that included data from clinical trials, sub-group analyses, follow-up qualitative studies with trial participants, more recent open-label demonstration projects, and pharmacokinetics strongly demonstrates that PrEP is a highly effective HIV-1 prevention strategy for women. More than thirty years into the HIV epidemic, oral PrEP is the first intervention that women can control themselves. The demonstrated effectiveness of PrEP for female HIV-1 prevention has been as high as 72-94% among women with high adherence [66, 95] and it is a cost-effective public health strategy for populations at high risk of HIV-1 acquisition [69, 71, 131], including among pregnant and breastfeeding women [70]. These favorable characteristics make time-limited PrEP

use during the pregnancy and postpartum periods a key factor in reducing female and pediatric HIV-1 incidence.

Delivery of PrEP to pregnant and postpartum women

As discussed in *Chapters 1-3*, since 2012, clinical guidance from multiple individual agencies have recommended the use of PrEP for individuals at high-risk of HIV-1 acquisition. While these recommendations have not excluded pregnant and postpartum women, much of the focus during time periods related to pregnancy has been directed toward mutually disclosed HIV-1 serodiscordant couples. To date, there has been less targeted implementation of programs offering PrEP to pregnant and postpartum women seeking care within routine public health services and with male partners of unknown HIV-1 status. Kenya has been on the forefront of adopting a public health population-based approach to PrEP implementation, focusing on geographic areas with high HIV-1 incidence and endorsing PrEP use among pregnant and breastfeeding women[180]. Conversely, in South Africa, where nearly a quarter of women of reproductive age are HIV-infected [181], tenofovir-based PrEP is considered contraindicated during pregnancy; women taking PrEP who become pregnant are advised to consider stopping and PrEP is not routinely offered to already pregnant or postpartum women [182]. In light of the initial debate surrounding PrEP efficacy for women and slow adoption of new medications during pregnancy and breastfeeding, it is groundbreaking that earlier this year, in July 2017, the World Health Organization published *Preventing HIV during Pregnancy and Breastfeeding in the Context of PrEP* specific guidance calling for the integration of PrEP into routine maternal and child health services and offered to pregnant and breastfeeding women in high HIV-1 prevalence settings [76]. It is incumbent upon the HIV-1 and reproductive health communities to leverage these guidelines for support at national and local levels and use this endorsement as momentum to accelerate implementation of enhanced HIV-1 prevention within existing reproductive health services.

Opportunities for HIV-1 prevention among HIV-1 affected couples who desire pregnancy

Effective antiretroviral-based HIV-1 prevention is also relevant to mutually disclosed HIV-1 serodiscordant couples, one specific target population than has known HIV-1 exposure and can experience specific time periods of increased HIV-1 risk. HIV-1 serodiscordant couples with fertility

desires experience heightened vulnerability to HIV-1 acquisition as they must intentionally forgo condom use during pregnancy attempts. In *Chapter 2*, we show that the risk of condomless sex was twice as high during the early pregnancy stage, which began at last menstrual period and therefore included sexual acts that resulted in pregnancy. ART for HIV-1 infected individuals has been found to reduce HIV-1 transmission by as much as 96% and may be a sufficient risk-reduction strategy for some couples throughout pregnancy. However, achieving HIV-1 viral suppression requires high adherence to ART from the HIV-1 infected individual, and many HIV-infected partners choose to delay the initiation of ART, even within the context of a mutually disclosed HIV-1 serodiscordant relationship [183]. Thus, enhanced safer conception, namely condomless sex timed to days with peak fertility and/or PrEP, can be warranted to reduce HIV-1 acquisition within relationships where the HIV-1 infected partner has not yet achieved viral suppression, and are important options for couples that may not have access to higher cost medically assisted reproductive technologies.

The results presented in *Chapter 4* describe the fertility desires and preferences for safer conception strategies among 150 heterosexual HIV-1 infected individuals in Seattle, WA, a population in which this research question had not yet been previously studied. We found that nearly a third of patients categorized as reproductive age reported wanting one or more children in the future. Among this subset of reproductive age participants with fertility desires, use of effective contraception and condoms was low, suggesting that there are opportunities to prevent unintended pregnancy and/or plan pregnancy attempts in a way that minimizes the risk of HIV-1 transmission.

Preconception counseling with providers is an important gateway for discussions about preventing onward transmission to partners during pregnancy attempts [163, 166, 184-187]., Yet prior studies have shown that HIV-1 providers do not proactively inquire about fertility desires and provide preconception counselling, and such conversations can be preempted by assumptions and questions specific to contraceptive use [172]. The results of *Chapter 4* support this finding. It is a concern only 25-35% of men and women in our study population reported that a healthcare provider had ever initiated a discussion with them on their fertility desires. Fertility desires are relevant to primary care, obstetrics and gynecology, and infectious disease, yet artificial distinctions between these fields and limited training on

safer conception contribute to gaps in care [167]. Providers have described time constraints during patient visits, competing priorities, and limited familiarity with how to discuss HIV-1 transmission risk during pregnancy and navigate the menu of safer conception strategies with patients as barriers to providing comprehensive safer conception counselling [167].

National guidance on safer conception options for HIV-1 serodiscordant couples from the US Centers for Disease Control and Prevention (CDC) has been dated and not reflective of current scientific knowledge until very recently. For the first time in twenty-seven years, the CDC distributed updated safer conception guidelines for HIV-1 serodiscordant couples in July 2017. The updated guidance revoked the previous emphasis on the need for sperm washing for HIV-1 infected men, but suggested that a couple must utilize multiple strategies simultaneously (i.e. ART and PrEP use combined with either timed condomless sex or medically assisted reproduction) to prevent HIV-1 transmission. Some couples may prefer and be able to successfully access multiple strategies, however, these guidelines overlooked consistent and robust epidemiological evidence that individual strategies alone (e.g. ART or PrEP) can prevent HIV-1 transmission when taken with high adherence and may be sufficient for some couples. In response to feedback from HIV-1 advocates, CDC promptly published an *erratum* one month later clarifying the effectiveness of individual ART and PrEP, however this example underscores the confusion that persists around best practices for HIV-1 serodiscordant couples and how patient-centered decision making is not always emphasized in clinical guidelines [188]. Other individual professional organizations have developed more holistic and evidence-based recommendations for counselling and referring HIV-1 serodiscordant couples who desire children [189], but more consistent implementation of these guidelines is needed across healthcare settings [160]. It is important that providers within primary care, obstetrics and gynecology, and infectious disease expand conversations with male and female patients to include discussions about fertility desires and follow with appropriate counseling about pregnancy planning or contraceptive options, depending on patient needs.

Acceptability of and barriers to PrEP use during periconception and pregnancy

The majority of available data on the acceptability of PrEP during the periconception and pregnancy stages comes from studies in high HIV-1 prevalence settings in Africa. HIV-uninfected women

who became pregnant during the Partners PrEP Study had high adherence to study medication during the periconception period, even when drug safety and efficacy were unknown [132]. In the Partners Demonstration Project, an open-label study which evaluated integrated delivery of PrEP and ART use among HIV-1 serodiscordant couples, pregnancy incidence was high, 88% of pregnant women elected to continue PrEP use after pregnancy diagnosis, and there were no female incident HIV-1 infections among pregnant women taking PrEP [78]. Within these studies, PrEP use among women with fertility intentions was high [190] and did not affect pregnancy incidence [17, 46, 112]. Among HIV-1 affected couples receiving safer conception services at a primary care clinic in South Africa, 44% of women have chosen to use PrEP during pregnancy attempts [191]. Furthermore, qualitative studies among members of African HIV-1 serodiscordant couples have confirmed that PrEP is a welcomed strategy for reducing HIV-1 transmission while achieving their fertility goals [154, 155, 176, 177, 192].

The data presented in *Chapter 4* add to the growing body of literature suggesting that PrEP is also an acceptable strategy for safer conception among HIV-1 affected couples in the United States. Among our study population of heterosexual HIV-1 infected individuals in Seattle, WA, willingness to use ART or PrEP to reduce HIV-1 risk during pregnancy attempts with a current or future HIV-1 uninfected partner was high (90.1% and 74.4%, respectively), and these two strategies were ranked as the top two preferred safer conception strategies. However, only 11% of participants that were part of a HIV-1 serodiscordant heterosexual relationship reported that their uninfected partner had experience using PrEP, a finding that is consistent with the observed low uptake of PrEP among heterosexual individuals at high risk of HIV-1 acquisition in the United States. The CDC estimates that 157,000 heterosexual men and 468,000 women in the US are candidates for PrEP [193], however use of this prevention strategy has been primarily been concentrated among men who have sex with men. Women have especially be overlooked in the promotion of PrEP as an HIV-1 prevention strategy. In a recent survey among 1,700 women receiving care at a family planning clinics in California, 74% of women who met CDC eligibility for PrEP (87/118) had never heard of PrEP [194].

In our *Chapter 4* study, the most frequently reported barriers to PrEP use included not knowing about PrEP, cost, and the safety to HIV-1 uninfected partners and infants. These factors are similar to

clinical, system-level, and cost concerns that providers in the US have reported as reported as reasons for low prescription of PrEP for HIV-1 serodiscordant couples [168]. Safer conception programs need to incorporate messages to normalize and address the most commonly cited barriers, including introducing the concept of antiretroviral use by HIV-1 uninfected individuals for HIV-1 prevention, sharing data on the demonstrated efficacy and safety of PrEP, including during pregnancy, and options to address the cost of PrEP. Cost associated with initiating and maintaining PrEP include payment for clinical assessment, laboratory tests, and the medication. Resources developed by public health agencies, such as the CDC and the Washington State Department of Health, are available to help patients and healthcare providers navigate decisions regarding PrEP initiation, including information on efficacy, eligibility, and payment assistance programs [195, 196].

Current gaps in knowledge of how to deliver PrEP to pregnant and postpartum women

Ongoing research and program implementation will provide data on PrEP uptake, continued use, and effectiveness when integrated into antenatal and postnatal clinics, targeting pregnant women and male partners [79, 80, 197]. One challenge to implementation is identifying women who are at high risk for HIV-1 acquisition during pregnancy and breastfeeding to avoid unnecessary PrEP use among those whose HIV-1 risk is very low or non-existent. Many pregnant woman do not know the HIV-1 status of their partners, a key factor in understanding their risk of HIV-1 exposure and acquisition. In a recent prospective cohort study of HIV-1 uninfected pregnant women attending antenatal care in western Kenya, only 30% of women were aware of their male partner's HIV-1 status [58]. Another study in Kenya found that 7% of women who tested HIV-1 negative at their first antenatal care visit unknowingly had an HIV-1 infected male partner, and only learned their partner's status when men were specifically targeted by clinic or home-based couples testing and counselling [198]. A recently developed empiric risk scoring tool uses routinely collected antenatal data to assist providers to objectively identify women at high risk of HIV-1 acquisition during pregnancy and postpartum [199]. In clinic settings where this tool can be incorporated into the existing workflow, the results can facilitate targeting women at high risk of HIV-1 with enhanced prevention counselling, including the option to initiate PrEP, to those who need it the most.

Implementation studies should prioritize collection of additional longitudinal data to inform effective strategies for promoting high adherence among pregnant and postpartum women whose self-perceived risk may be different than that of women with known HIV-1 infected male partners, and, as is feasible, continue informing the maternal and infant safety profile of PrEP. As discussed in *Chapter 3*, pharmacokinetic studies demonstrate that more consistent adherence to daily oral tenofovir-based PrEP is required for women to achieve sufficient drug concentrations in the female genital tract than is required for men, especially in the presence of other factors such as immature genital mucosa that may increase HIV-1 susceptibility among younger women. It is overwhelmingly clear that the effectiveness of daily oral tenofovir-based PrEP is dependent on adherence; in the three studies where overall adherence was high efficacy among all female study participants was 49-71% and efficacy was 75-94% in subgroups of females with high adherence. As we assert in *Chapter 3*, rather than providing evidence to delay the implementation of PrEP, these results underscore the value of accelerating delivery PrEP to women at high risk of HIV-1 acquisition within programs that support high adherence.

While the exact dosing requirements for women are not yet known, sufficient adherence may be especially important during pregnancy, when physiological changes contribute to faster metabolism of many drugs. Data from studies of tenofovir-based ART used by HIV-1 infected pregnant women suggest that clearance of tenofovir is higher and concentrations of tenofovir are lower during pregnancy, although these difference have not yet led to recommendations to increase the dosage of tenofovir-based ART during pregnancy [200-202]. Future studies of the pharmacokinetics of tenofovir-based PrEP during pregnancy are needed, and in the interim, PrEP during pregnancy should be offered in parallel with sufficient counselling and support services to facilitate high adherence.

Longer-acting formulations of antiretrovirals for HIV-1 prevention, such as the dapivirine vaginal ring [203] and cabotegravir and rilpivirine injectables currently under investigation [204-206], may provide pregnant women with tools to prevent HIV-1 acquisition without the need for daily medication. One key principle of biomedical research is “do no harm”, and this is especially imperative among pregnant women, fetuses, neonates, and infants, all of whom are universally considered vulnerable populations in human research. Pregnant and postpartum women are often excluded from research, in part due to the

increased burden of human subject protections that are intended to protect this vulnerable population, but these exclusions ironically prevent or significantly delay the delivery of prevention tools to those that need them the most [207-210]. Research on longer-acting PrEP agents should seek to evaluate these strategies among pregnant women as early as is feasible after the establishment of safety and efficacy in non-pregnant women.

Identification of incident maternal HIV-1 infections during pregnancy and postpartum

Lastly, if female HIV-1 acquisition during periconception, pregnancy, and postpartum cannot be prevented entirely, efforts to identify incident maternal infections during these time periods must be increased in high HIV-prevalence settings. While routine HIV-1 testing of pregnant women has increased substantially in recent years and many high burden countries have achieved the WHO target of 95% of pregnant women knowing their status, the vast majority of this testing occurs at the first antenatal care visit [88, 211]. Low repeat maternal testing during pregnancy and postpartum is a missed opportunities to identify incident maternal infections and women at high risk perinatal transmission [212, 213]. Although WHO recommends at least one repeat HIV-1 test during pregnancy, labor, or postpartum for women living in generalized HIV-1 epidemics [88] these current guidelines lack specificity in terms of when to test, are inconsistently implemented, and insufficient for timely identification and treatment of acute HIV-1, resulting in missed opportunities to identify incident maternal and pediatric infections. Kenyan healthcare providers interviewed for a recent qualitative study cited supply of test-kits, unawareness of guidelines, workload, lack of prompts in medical registers, and late presentation or limited participation in antenatal care as barriers to implementing repeat-testing [89].

Given the high risk of HIV-1 acquisition during pregnancy, especially in late pregnancy as was presented in *Chapter 2*, more specific normative guidance on repeat testing is urgently needed, followed by strategies that integrate repeat-testing into routine antenatal and postnatal care. Specifically, repeat maternal HIV-1 testing during the postnatal period has received less attention. This is of concern given our finding that the per-act risk of HIV-1 acquisition was highest during postpartum, nearly four-fold higher than during time not related to pregnancy. Integrating repeat maternal HIV-1 into standard childhood immunization schedules in a way that leverages existing engagement in clinic-based services and

promotion of maternal HIV-1 self-testing are innovative strategies that can identify incident HIV-1 infections during breastfeeding and prior to a subsequent pregnancy.

Conclusion

The three studies included in this dissertation have quantified the risk of female HIV-1 acquisition in different reproductive stages, made the case for PrEP as a highly efficacious HIV-1 strategy for women, and assessed the fertility intentions and willingness to use safer conception strategies during pregnancy attempts among HIV-1 infected individuals. To date, women have been disproportionally affected by the HIV-1 epidemic, and are especially vulnerable to HIV-1 acquisition during time periods surrounding pregnancy. Given this increased risk of HIV-1 acquisition, coupled with the potential risk for onward perinatal transmission in the event of incident maternal HIV-1 infection, it is essential that the HIV-1 and reproductive health communities work together to increase the delivery and uptake of effective HIV-1 prevention strategies for women of reproductive age. PrEP is one highly-effective prevention strategy that women can benefit from, but it needs to be delivered in a way that fits with women's lives and preferences. Women are often motivated to prioritize health immediately before, during, and after pregnancy, and successful prevention of HIV-1 during these times will have a lasting impact on maternal and infant health. Increasing safer conception counselling and strategies for known HIV-1 serodiscordant couples and integrating PrEP as a primary HIV-1 prevention strategy into routine antenatal and postnatal care are optimal next steps to reduce HIV-1 acquisition during the periconception, pregnant, and postnatal periods.

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VITA

Kerry Thomson completed a PhD in Epidemiology at the University of Washington in December 2017. Her research has focused on the risk of female HIV acquisition during the periconception, pregnancy, and postpartum periods and the use of enhanced HIV prevention, including pre-exposure prophylaxis (PrEP), during these time periods. Prior to starting graduate studies at the University of Washington, Kerry Thomson earned a Master of Public Health (Global Health) from Emory University, worked on maternal and child health and chronic disease prevention at local, state, and federal public health agencies in the United States, and worked as a field epidemiologist in Kenya and South Sudan for Médecins San Frontiéres.