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PrEP as Peri-conception HIV Prevention for Women and Men

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Abstract Daily oral tenofovir (TDF)-based pre-exposure prophylaxis (PrEP) is an effective HIV prevention strategy and recommended for men and women with substantial risk of HIV acquisition. The peri-conception period, the stage prior to pregnancy when condom use is necessarily reduced, has elevated HIV risk that can be mitigated by PrEP use. Data from a randomized trial suggest that peri-conception PrEP use by HIV-seronegative women does not increase the risk of pregnancy loss, birth defects or congenital anomalies, preterm birth, or infant growth faltering. Women considering PrEP use throughout pregnancy must weigh the known increased risk of HIV acquisition with unknown risks of drug effects on infant growth. PrEP has been used safely by HIV-seronegative men with HIV-seropositive female partners who have become pregnant. As an effective user-controlled HIV prevention strategy, PrEP offers autonomy and empowerment for HIV prevention and can be recommended alongside antiretroviral therapy, fertility screening, vaginal self-insemination, intercourse timed to peak fertility, medically assisted reproduction, and other safer conception strategies to provide multiple options. The integration of PrEP into safer conception programs is warranted and will safely reduce HIV transmission to women, men, and children during the peri-conception period.

Keywords Pre-exposure prophylaxis · PrEP · HIV prevention · Pregnancy · Peri-conception · Safer conception · Science of prevention · Review

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Introduction

Peri-conception—the period leading up to pregnancy—is a time of increased HIV risk for men and women having condomless sex that results in pregnancy [1, 2]. For individuals with risk of HIV acquisition, daily oral tenofovir (TDF)-based pre-exposure prophylaxis (PrEP) is an effective HIV prevention strategy with US Food and Drug Administration approval and endorsement in the World Health Organization (WHO) guidelines on antiretroviral use [3–6]. PrEP offers personal autonomy over HIV prevention, not requiring negotiation or a partner's knowledge of use and is now being

delivered in the USA while implementation strategies are being developed in many other settings. Co-formulated emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) is the medication approved for HIV prevention and commonly prescribed as a component of multi-drug HIV treatment regimens. A recent analysis explored the numbers needed to harm for PrEP and aspirin and concluded that PrEP favorably compares with aspirin [7].

Concerns have been raised about PrEP use during pregnancy attempts by HIV-seronegative women because of the potential for adverse pregnancy and infant outcomes that could result from in utero antiretroviral exposure [8, 9]. Due to the timing of pregnancy confirmatory testing at least 2 weeks after condomless sex and the recommendation to continue PrEP for at least 1 month following HIV exposure, peri-conception PrEP use would be followed by, at least, some use in early pregnancy [10]. PrEP use would also extend for women who choose PrEP as a prevention strategy during pregnancy and/or breastfeeding. The purpose of this review is to provide an update on PrEP safety during peri-conception, in terms of pregnancy and infant outcomes, and offer strategies for implementing PrEP as a peri-conception HIV prevention strategy for women and men.

Peri-conception PrEP Use—Including Use During Early Pregnancy—Is not Associated with Adverse Effects on Pregnancy Outcomes or Infant Growth

Safety data on peri-conception PrEP use and its effect on pregnancy outcomes and infant growth are available from three randomized trials conducted to estimate the efficacy of PrEP for HIV prevention (Table 1) [11, 13, 14]. FTC/TDF is a pregnancy category B medication, with no evidence of harm in animal studies but no adequate, well-controlled studies in pregnant women [16] and in line with this classification, clinical trials withheld study drug when women had a positive pregnancy test at the study clinic. In the Partners PrEP Study, 1785 HIV-seronegative women with HIV-seropositive male partners from Kenya and Uganda experienced 431 pregnancies throughout the 3-year follow-up period [13]. On average, women had an estimated 35 days of exposure to tenofovir (as FTC/TDF or single formulation TDF) during early pregnancy in addition to exposure between study enrollment and pregnancy. There were no differences in birth outcomes or infant growth indicators measured at 1 year after birth. A slightly elevated frequency of pregnancy loss among women using FTC/TDF (42.5 % of pregnancies versus 32.3 % in the placebo arm) was not statistically significant and not mirrored by women using TDF. This rate of pregnancy loss has been seen in other studies with sensitive testing that detects early pregnancy [17]. Two additional PrEP clinical trials, FEM-PrEP conducted among 2120 women in Kenya, South Africa, and Tanzania and VOICE among 3019 women from South Africa, Zimbabwe, and Uganda, observed substantial numbers of pregnancies among women randomized to active PrEP agents as well as placebo and observed no indications of pregnancy-related safety concerns among those in the active PrEP arms [11, 12, 14, 15]. However, adherence to daily PrEP medication was extremely low in these two trials and results based on randomization arm would be better supplemented by data from the subgroup of women who were highly adherent [12, 15].

HIV-seronegative men with HIV-seropositive female partners in the Partners PrEP Study ($n = 2962$) who were randomized to active PrEP agents did not experience adverse effects of PrEP on male fertility or pregnancy outcomes in their female partners [18]. The pregnancy incidence rate among HIV-seropositive women with male partners using active PrEP agents was similar to those using placebo (12.4 per 100 person-years among those randomized to FTC/TDF, 13.2 among those randomized to TDF, and 13.2 among those randomized to placebo), pregnancy losses occurred with similar frequency, and there was no difference in gestational age at birth or in early pregnancy losses.

Though few studies have examined PrEP safety during peri-conception periods, data from a robust randomized trial do not suggest adverse effects of using PrEP during peri-conception on pregnancy outcomes or infant growth when used by HIV-seronegative women or men. A number of questions remain regarding how to deliver PrEP for individuals entering a peri-conception period, including people who will have an unintended pregnancy as well as those with declared pregnancy intent. Outstanding questions include whether peri-conception PrEP is safe to continue throughout pregnancy and breastfeeding, whether PrEP is valued by women and men as a peri-conception strategy and will be used with sufficient adherence, whether there is an additive benefit of PrEP use when an HIV-seropositive partner is using antiretroviral therapy (ART) and virally suppressed, and how to identify individuals who would benefit from peri-conception PrEP use.

Should Peri-conception PrEP Used by Women Be Continued During Pregnancy and Breastfeeding?

For many women, PrEP use during the peri-conception period would extend naturally into pregnancy and breastfeeding periods, when HIV risk remains high and prevention efforts extend the benefit to the fetus and child. To date, the only source of data from HIV-seronegative women using a PrEP agent (TDF) throughout pregnancy is from women using it for hepatitis B treatment. A 2016 meta-analysis of three non-randomized studies among approximately 240 women found no association of prenatal tenofovir use with congenital malformations, prematurity, or Apgar scores [19–22].

In the absence of substantial data from HIV-seronegative women using TDF as PrEP throughout pregnancy, data can be

Table 1 Longitudinal studies presented in 2014–2015 examining the safety of peri-conception daily oral PrEP use among HIV-seronegative women

Study name Lead author	Study design	Population	Daily oral PrEP agent	PrEP adherence (plasma TDF in random sample)	Safety data on pregnancy outcomes	Safety data on infant outcomes
FEM-PrEP Callahan 2015 [11, 12]	Randomized trial	2120 women from Kenya, South Africa and Tanzania; 125 pregnancies	FTC/TDF	24 %	• Pregnancy incidence of 11.4 FTC/TFD and 7.7 placebo; higher pregnancy incidence in FTC/TDF group is related to poor adherence to oral contraceptives • Of 115 pregnancies with outcome data, 30 had some complication, no difference observed by arm (vaginal bleeding was most common complication)	No data collected
Partners PrEP Study Mugo 2014 [4, 13]	Randomized trial	1785 women from Kenya and Uganda; 431 pregnancies	Separate arms f or FTC/TDF and TDF	81 % FTC/TDF 83 % TDF	• No difference in rates of pregnancy incidence per 100 person-years (FTC/TDF 8.8 [$p = 0.39$ versus placebo]; TDF 11.9 [$p = 0.22$ versus placebo]; placebo 10.0) • No significant difference in rates of pregnancy loss (FTC/TDF 42.5 % [$p = 0.16$ versus placebo]; TDF 27.7 % [$p = 0.46$ versus placebo]; placebo 32.3 %)	• Preterm birth (FTC/TDF 8.7 % [$p = 0.85$ versus placebo]; TDF 2.5 % [$p = 0.16$ versus placebo]; placebo 7.7 %) • Congenital anomaly (FTC/TDF 8.5 % [$p = 0.51$ versus placebo]; TDF 4.9 % [$p = 0.86$ versus placebo]; placebo 7.6 %) • No difference in 1-year infant growth parameters
VOICE Bunge 2015 [14, 15]	Randomized trial	3019 women from Uganda, South Africa and Zimbabwe included to study oral PrEP agents; 452 pregnancies	Separate arms for FTC/TDF and TDF	29 % FTC/TDF 30 % TDF	• No difference in pregnancy incidence per 100 person-years (FTC/TDF 8.0; TDF 7.4; placebo 7.9) • No difference in pregnancy loss (FTC/TDF: 3 % TDF 0 %; placebo 6 %) • No difference in any pregnancy outcomes (premature birth, stillbirth, spontaneous abortion, ectopic pregnancy, or elective abortion)	Ten (10) instances of small for gestational age (breakdown by arm not provided)

leveraged from HIV-seropositive women who used TDF as part of multi-drug ART. A 2013 comprehensive review that included six clinical studies of nearly 900 HIV-seropositive women and five studies of over 700 children with in utero tenofovir exposure due to maternal prenatal TDF use concluded that TDF is generally safe for use by HIV (and/or hepatitis B)-infected pregnant women [23]. In this review, data from one study raised concerns: infants exposed to maternal combination antiretroviral regimens that included TDF were slightly shorter at 1 year, although the difference, 0.17 cm on average, is unlikely to be clinically significant [24].

Since 2013, six studies of HIV-seropositive women using TDF as part of multi-drug ART regimens have presented results (Table 2) [25–30]. In a randomized study of 3529 African and Indian women designed to assess the safety and efficacy of triple-drug ART (versus a single drug regimen) for prevention of perinatal HIV transmission, overall findings support WHO recommendations that triple-drug HIV treatment regimens be used [25]. Unexpected safety findings included two results that merit further critical study: women randomized to TDF/FTC-lopinavir/ritonavir (LPVr) had significantly higher rates of very early preterm birth than those receiving zidovudine (AZT)-lamivudine (3TC)-LPVr or AZT alone (6 % in the TDF-containing arm versus 3 % in the other two arms) and infant death (4.4 % versus 0.6 %, $p = 0.001$) [25]. These differences may be driven by drug interactions between tenofovir and ritonavir but further follow-up is needed [31]. In another study, bone mineral content was reduced among 74 infants exposed to ART regimens that included TDF relative to 69 infants exposed to ART regimens that excluded TDF. [26] The magnitude of difference, a 12 % reduction in bone mineral content, has unknown clinical significance but is a greater loss than observed in studies of changes in adult bone mineral content following TDF initiation [5, 32]. Further evaluations to determine the clinical significance and persistence of infant bone mineral content loss following exposure to maternal TDF use are important as well as research to understand whether there are clinical differences in these outcomes among women using TDF for HIV prevention versus treatment. Other studies of infants with exposure to maternal TDF use have not seen differences in infant growth parameters or congenital anomalies, although the studies are often small and use non-randomized designs [28, 29, 33]. A recent study of 58 HIV-exposed uninfected infants whose mothers used TDF prenatally was assessed with DXA scans within 1 month after birth and concluded that fetal tenofovir exposure duration and timing was not associated with infant meconium TFV concentrations, weight, length, or bone mineral content [30].

Data from women using TDF during breastfeeding, as PrEP or HIV treatment, are scarce. PrEP clinical trials withheld study drug during breastfeeding, HIV-infected women in developed countries are generally advised not to breastfeed, and data from breastfeeding women using TDF in developing countries have not been captured [34]. Small studies of hepatitis B-infected women using TDF during pregnancy and early postpartum have measured levels of tenofovir in breastmilk to be lower than the maternal serum or cord blood levels, suggesting that the impact of tenofovir exposure on bone health and renal function during breastfeeding would be less than during pregnancy [35, 36]. Pharmacokinetic data from mother-infant pairs will provide important information about the amount of tenofovir that maternal PrEP use transfers to infants through breastfeeding.

Limited data on PrEP use during pregnancy and breastfeeding are largely reassuring but raise questions about the possibility for an effect of TDF on early infant growth parameters that may or may not have clinical significance. For women considering PrEP use in pregnancy, these uncertain risks must be weighed against the increased risk of HIV acquisition during pregnancy and the subsequent increased risk of perinatal transmission during acute HIV infection. Observational analyses suggest that pregnancy-induced immune, hormonal, and behavioral changes may increase HIV susceptibility, and acute HIV infection during pregnancy has significant consequences for the baby and mother [1, 2, 37–39]. Acute HIV infection during pregnancy and postpartum poses a double burden as acute maternal HIV infection accounts for 26 % of perinatal HIV transmission [40, 41]. Thus, for women exposed to HIV during pregnancy, the consideration of PrEP-induced adverse outcomes with unknown clinical significance must be weighed against the known consequences of HIV infection for mother and child and the benefits that PrEP would provide to reduce HIV risk. This risk-benefit calculus is recognized in the US CDC and WHO guidelines for women using PrEP who become pregnant, including the recommendation to counsel on the risks and benefits of continuing PrEP use during pregnancy alongside consideration of the ongoing risk of HIV acquisition and transmission to infants born to a mother who becomes infected during pregnancy or breastfeeding [42, 43].

Do Women and Men Vulnerable to HIV Infection Value PrEP as a Peri-conception HIV Prevention Strategy?

HIV-seronegative women and men can use a range of interventions to reduce HIV risk while attempting pregnancy including antiretroviral-based strategies (PrEP and/or ART use by HIV-seropositive partners), fertility care and assisted reproduction, medical male circumcision, treatment of genital infections, self-insemination when the male is HIV-seronegative, and limiting condomless sex to days with peak fertility to reduce HIV exposure [44]. Many of these safer conception options can be combined based on preferences and access to these methods. Among European studies of safer conception for HIV-serodiscordant couples, most HIV-seronegative

Table 2 Studies presented in 2014–2015 examining the pregnancy-related safety of tenofovir-containing antiretroviral therapy regimens used by HIV-seropositive women

Study name Lead author	Study design	Population	Antiretroviral regimen	Safety data on pregnancy outcomes	Safety data on infant outcomes
PROMISE Fowler [25]	Randomized trial	3529 women from 14 sites in Africa and India; analysis includes 1229 pregnancies	Arm A: ZDV + single dose NVP at delivery + TDF/FTC tail Arm B: ZDV-3TC + LPVr Arm C: TDF/FTC + LPV-RTV	Elevated rate of very early (<34 weeks) preterm birth in the TDF/FTC + LPV-RTV arm (relative to arms A and B)	Elevated rate of neonatal death among infants born to women in the TDF/FTC + LPV-RTV arm (relative to arm B)
SMARTT within the Pediatric HIV/AIDS Cohort Study Siberry [26]	Cross-sectional	143 HIV-exposed uninfected infants	Mothers received ≥8 weeks of multi-drug regimens during pregnancy; 74 infants exposed to TDF-containing regimens were compared to 69 infants without TDF exposure	Not assessed	No difference in gestational age, mean length or weight Mean bone mineral content was reduced (by an average of 5.3 g, a 12 % reduction) in TDF-exposed infants
Pintye [27]	Cross-sectional	277 HIV-exposed uninfected infants	Mothers used 3-drug combination regimens; 89 infants with TDF exposure were compared to 188 without TDF exposure	Not assessed	No difference in weight-for-length, length-for-age, and head circumference-for-age Z-scores Modest reduction in infant weight-for-age Z-score at 6 weeks likely explained by differences in demographic characteristics
Liotta [28]	Observational prospective cohort	103 mother-infant pairs	All women used TDF + EFV + 3TC for at least 6 weeks in third trimester and postpartum	Not assessed	Levels of bone formation and bone absorption were similar to reference pediatric standards
SMARTT within the Pediatric HIV/AIDS Cohort Study Williams [29]	Retrospective cohort	2580 HIV-exposed uninfected children from the US	Multiple regimens were observed	Not assessed	Levels of congenital anomalies were generally high but not different between infants exposed to maternal ART, including TDF
SMARTT within the Pediatric HIV/AIDS Cohort Study Himes [30]	Retrospective cohort	58 HIV-exposed uninfected infants from the US and Puerto Rico	≥8 weeks of TDF in the third trimester of pregnancy	Increased meconium tenofovir concentrations were associated with greater gestational ages at birth	Meconium tenofovir concentrations were not associated with bone density or any growth outcome

ZDV zidovudine, *NVP* nevirapine, *TDF* tenofovir, *FTC* emtricitabine, *3TC* lamivudine, *LPV* lopinavir, *RTV* ritonavir

women with virally suppressed HIV-seropositive male partners consistently used PrEP with peri-coital dosing as a safer conception strategy [45, 46]. In the Partners PrEP Study, women who became pregnant maintained consistent use of PrEP prior to pregnancy, indicating dedication to the clinical trial goals and willingness to use an experimental drug during pregnancy attempts [47]. Qualitatively, women in HIV-serodiscordant couples enrolled in the Partners PrEP Study expressed desire for strategies like PrEP to reduce peri-conception HIV risk due to fear of HIV transmission within the couple during pregnancy attempts [43]. In an open-label delivery study of daily oral PrEP, women maintained high adherence to PrEP in the period immediately preceding pregnancy [48].

PrEP may be used as a time-limited strategy, with use limited to periods with greatest vulnerability to HIV infection. South African women seeking HIV counseling and testing or HIV care have reported that PrEP is an acceptable safer conception strategy as long as it is not a lifelong intervention [49]. Peri-conception PrEP use, with the possibility to continue during pregnancy, is an example of a time-bound period during which PrEP use with high adherence is desirable, acceptable and feasible. Given the common desire for pregnancy and children and demonstrated interest in peri-conception HIV prevention, there is a high valuation of PrEP and willingness to incorporate it into safer conception strategies.

Is There an Additive Benefit of PrEP Use when ART Use by HIV-seropositive Partners Is such a Powerful Prevention Strategy and a Priority Intervention?

ART is an important health-preserving, infection-controlling intervention for HIV-seropositive individuals. Furthermore, when HIV viremia is suppressed by ART, the risk of transmission to partners is thought to be zero, making ART a powerful tool for prevention as well as treatment [50, 51]. WHO guidelines recommend that all HIV-seropositive individuals initiate lifelong ART immediately after diagnosis, regardless of clinical stage or immune status [43]. Given the effectiveness of ART as prevention, PrEP use in parallel by an HIV-seronegative partner is unlikely to further reduce a negligible amount of HIV risk and is not cost effective [52, 53]. However, aversion to ART initiation is common among newly diagnosed and healthy HIV-seropositive individuals and a robust literature describes myriad challenges to sustaining adherence levels that are sufficient to sustain viral suppression [54–59]. Furthermore, ART use by HIV-seropositive partners is not an effective prevention strategy when an HIV-seronegative person has other partners not using ART. For individuals with multiple partners, PrEP offers protection to the seronegative partner when ART is not used (or is not known to be used) by all HIV-seropositive partners or when additional partners are greatly vulnerable to HIV acquisition.

An important goal of HIV prevention is to offer individuals a range of prevention options and support the choice of one or more strategies. For women and men seeking safer conception services, the decision to use PrEP can reflect individual preferences. While immediate pregnancy intentions may present an opportunity to motivate ART initiation and sustained use among HIV-seropositive men and women, individuals ultimately choose HIV prevention strategies based on their current situation, personal risk perceptions, and desired degree of control over their own HIV risk. In sub-Saharan African settings, 30–80 % of newly pregnant women are unaware of their partner's HIV status and <20 % involve partners in HIV testing, underscoring an urgent need for women-controlled approaches for peri-conception HIV prevention [60–66]. For a woman who does not know her partner's status and is not able to negotiate HIV testing, status disclosure, and/or ART use, PrEP is a method she may utilize to realize reproductive goals while controlling her own HIV risk [67, 68].

How Can Programs Identify Individuals Who May Benefit from Peri-conception PrEP?

Current efforts to integrate sexual and reproductive health programs with HIV prevention programs offer opportunities for holistic counseling that includes pre-conception planning, peri-conception care, and contraception [69, 70]. When providers initiate discussions about reproductive goals and pregnancy planning, they can offer individuals HIV prevention options that align with their personal goals for family building or delaying pregnancy. HIV care providers can also identify HIV-seropositive individuals with HIV-seronegative partners and provide information about safer conception options, including PrEP and linkages to access PrEP. For women wishing to prevent or delay pregnancy, PrEP does not interact with hormonal contraceptives; family planning clinics present opportunities to integrate counseling on safer conception and HIV prevention including PrEP [71, 72]. Because many individuals may not be able to disclose HIV status and/or bring their partner to a clinic, sexual and reproductive health and HIV prevention programs need to cater to individual-level as well as couple-based consultation [73]. Male-friendly environments may promote male health-seeking behaviors, including engaging in pre-conception care [74].

Discussions about fertility desires are not routinely included in HIV prevention counseling, presenting missed opportunities for provider-initiated discussion. In an ideal world, providers would assess reproductive goals for all of their HIV-affected clients. However, given the reality of time constraints, scoring tools may assist providers to identify individuals and couples likely to benefit from pre-conception counseling. Tools have been developed to identify women and HIV-serodiscordant couples with high HIV transmission risk and for couples with high pregnancy likelihood [75–77]. These

tools synthesize easily captured demographic and clinical information in order to efficiently identify and engage individuals and couples who may benefit from peri-conception HIV prevention and trigger provider-initiated discussion.

Conclusion

PrEP is an important peri-conception HIV prevention strategy and women and men value PrEP as an option to reduce HIV risk during pregnancy attempts. Safety data from clinical trials do not indicate any likelihood of harm to the pregnancy or infant growth when PrEP is used during the peri-conception period by women or men. Safety data—particularly related to infant growth—from infants with in utero exposure to PrEP throughout pregnancy and breastfeeding are incomplete. But from current data, women should have the opportunity to weigh the risks of acute HIV infection during pregnancy against the known benefits and unknown risks of PrEP.

Client-centered recommendations about all peri-conception HIV prevention strategies are essential. ART use has powerful benefits to prevent HIV transmission but counseling guidelines to relay information about these benefits must be strengthened to improve understanding and realization of this benefit. Strategies for HIV-serodiscordant couples that integrate ART use with time-limited PrEP during periods with greatest vulnerability to HIV are highly effective and need to be widely implemented [78]. Elevating discussion about HIV treatment as a prevention strategy into mainstream prevention counseling is a priority and this may be important to help HIV-seronegative individuals make decisions about adjunctive PrEP use. But even when HIV-seropositive partners are using ART, men and women may still want to augment their prevention with PrEP or other safer conception strategies and providers can support these choices. Furthermore, the inclusion of PrEP as an option for safer conception provides a user-controlled method for individuals who cannot rely on a partner to test for HIV or initiate and adhere to ART.

For women and men, PrEP offers individual control and a safe strategy to prevent sexual transmission during pregnancy attempts. Programs to deliver HIV prevention interventions to individuals desiring pregnancy are developing in many locations and international guidelines now recommend PrEP as a key strategy for individuals with substantial HIV risk [43]. Novel research will fill gaps in our understanding about the effects of PrEP on long-term child growth and bone health, the uptake and adherence to PrEP by women and men using PrEP for peri-conception HIV prevention, and best models for integrating PrEP delivery into existing reproductive health services. Ultimately, the integration of PrEP as a peri-conception HIV prevention strategy is a tremendous opportunity to promote safer conception, personal empowerment, and healthy reproductive decision-making.

Compliance with Ethical Standards

Conflict of Interest Renee Heffron is the Principal Investigator for a study that has received donated FTC/TDF from Gilead Sciences LLC. Jillian Pintye, Lynn T. Matthews, Shannon Weber, and Nelly Mugo declare that they have no conflict of interest.

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