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Challenges, risks, and opportunities of antiretroviral drugs in women of reproductive potential

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Abstract

Introduction: The HIV/AIDS epidemic has been one of the greatest challenges in global health, significantly affecting women of reproductive potential. Considerable advances in antiretroviral therapy for women living with HIV have contributed to improvements in quality of life, better reproductive and birth outcomes, and a reduced risk of perinatal transmission.

Areas covered: Despite the progress made, persistent challenges in access and adherence to antiretroviral drugs may limit their benefits for some women. More pharmacokinetic and safety studies in pregnant and lactating women are urgently needed, as are prospective surveillance systems to evaluate associations between fetal and infant antiretroviral exposures, drug–drug interactions, and pregnancy outcomes.

Expert opinion: Multipurpose technologies, such as combined HIV and other STI or unintended pregnancy prevention, and innovative delivery methods, such as the development of long-acting antiretrovirals, have the potential to reduce adherence challenges and enhance quality of life for women with HIV. Parallel advances in drug safety testing and surveillance are needed to ensure the health and safety of women with or at risk for HIV and children at risk for perinatal transmission.

Keywords

Antiretroviral; women; HIV; reproductive age; pregnancy; infant feeding; breastfeeding

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1. Introduction

Since it was first recognized in 1983, HIV has been one of the greatest challenges in global health. At the end of 2022, there were about 39 million persons with HIV worldwide, with a vast majority in sub-Saharan Africa [1]. Though the first reported cases primarily occurred from male-to-male transmission (MSM), heterosexual transmission has become the predominant mode of HIV transmission worldwide.

Globally, women of reproductive potential are at a disproportionate risk for HIV acquisition, especially in sub-Saharan Africa, where women account for up to 63% of new infections [2]. In comparison, in 2019, women accounted for 18% of new HIV diagnoses in the United States [3].

Children born to women with HIV are also at risk for acquiring HIV through perinatal transmission in utero, through delivery, or postnatally through breastfeeding. In the United States, the first case of perinatal HIV transmission was reported in 1982 [4], with cases peaking in 1992 [5]. By the end of 1993, nearly 15,000 children in the United States were diagnosed with perinatally acquired HIV [6], with an estimated mortality rate of 7.2 per 100 person years in 1994 [7]. In 1994, zidovudine (ZDV) was shown to be effective in preventing perinatal transmission when used prenatally, during labor/delivery and postpartum [8]. Subsequent advances in ARV treatments led to significant progress in reducing rates of perinatal transmission, with an estimated 1.5 million new infections in children prevented between 2010 and 2019 [9]. Rates of perinatal transmission have significantly decreased in high-income countries, with the United States achieving its elimination goals of fewer than 1 case of perinatal HIV per 100,000 live births and a perinatal transmission rate of <1% in 2019 [10]. Some European countries achieved similar milestones in previous years, including France and the UK [11] and Spain [12]. Many nations in sub-Saharan Africa have also shown significant declines in perinatal transmission between 2010 and 2019, particularly in eastern and southern Africa [13]. However, other regions still have relatively high perinatal transmission rates, particularly the Middle East and North Africa, Asia and the Pacific, and Western and Central Africa [13]. Furthermore, cases of perinatal transmission still occur in high-income countries, often due to unknown HIV status in the mother, difficulties in healthcare access, or challenges with ART adherence [14]. Additionally, despite the progress made in reducing perinatal transmission, in some countries the incidence of HIV in young women of childbearing age has increased [13], highlighting an ongoing need for expanded access to HIV prevention, testing, and treatment for women with reproductive potential. People of reproductive potential with HIV face different challenges in different settings.

2. Antiretroviral therapy in women of reproductive potential

2.1. Historical context

The recognition of the HIV epidemic sparked global efforts to develop treatments and ways to prevent new infections. A key advancement in the history of HIV treatment was the combination ART, typically consisting of two NRTIs, along with at least one drug from another class such as NNRTIs, PIs, or integrase strand transfer inhibitors (INSTIs). ART

was able to reduce HIV-associated morbidity and mortality, restore and preserve immune function, suppress viral load, and prevent sexual and perinatal transmission of the virus [15]; as a result, both length and quality of life dramatically improved [16]. For people of reproductive potential, this often meant that they can exercise reproductive autonomy for planning their pregnancies while avoiding perinatal HIV transmission. Today, the FDA has approved over 30 ARV drugs in eight different classes, with several co-formulated drug combinations. Of these, the U.S. Department of Health and Human Services (HHS) and the WHO have outlined certain preferred initial ARV regimens in ART-naïve pregnant women with HIV, including regimens with dual-NRTI backbones, INSTI regimens, NNRTI regimens and PI-based regimens with some differences in preferred regimens for different settings [17,18]. To optimize prevention of perinatal transmission, HIV diagnosis should be made and treatment should ideally be initiated prior to the pregnancy, and viral suppression maintained through pregnancy, labor/delivery and postpartum, during breastfeeding.

These milestones paralleled developments in ARVs for preventing perinatal HIV transmission. In 1994, interim results of a double-blind, randomized controlled trial led by the Pediatric AIDS Clinical Trial Group (PACTG) (Protocol 076), revealed a nearly 70% relative risk reduction of perinatal transmission among mothers with CD4 counts ≥200 cells/mm^3 who were treated with prophylactic ZDV during pregnancy, labor/delivery, and postpartum, compared to placebo [8]. Following these findings, ZDV was rapidly adopted in the United States and other countries as prophylaxis for perinatal transmission [19]; however, cost and resource constraints limited its implementation in low and middle-income countries with high HIV prevalence. In an effort to find simpler, less expensive, more easily implementable regimens for resource-constrained settings, several clinical trials tested other short course ARV regimens, which were shown to be effective in preventing perinatal transmission [20,21]. In 2015, the international Strategic Timing of Antiretroviral Therapy (START) study found that immediate ART initiation for non-pregnant adults with CD4 counts ≥500 cells/mm^3 was superior to delaying ART initiation until CD4 counts fall to 350 cells/mm^3 [22]. These findings revealed that prompt initiation of effective ART in women of reproductive potential was an essential strategy to improve women's health and curb perinatal transmission and highlighted the importance of increasing access to ART as treatment-as-prevention [23]. In 2014, UNAIDS and WHO announced the 90-90-90 targets for the end of 2020; 90% of people with HIV (PWH) in member nations were expected to know their HIV status; 90% of PWH would be receiving ART; and 90% on ART would be virally suppressed [24]. Even though these targets have not been met yet, expanding access to ART among women with HIV of childbearing potential further contributed to declines in perinatal transmission.

Today, ARVs play a central role across all stages of the perinatal transmission prevention cascade. As pre-exposure prophylactic agents, they reduce the risk of HIV acquisition for uninfected women; as ART for women with HIV, they ensure sustained viral suppression before, during, and after delivery; and they serve as peripartum and postpartum prophylaxis to mitigate perinatal transmission for pregnant women from 25% to 40% in the pre-ART era for non-breastfeeding and breastfeeding populations, respectively, to potentially less than 1% in the ART era [10,25]. Strategies to ensure adequate access and adherence to ARVs for women of childbearing potential should remain a critical national and global

priority. In this review, we will discuss considerations for use of ARV agents for people of reproductive potential, including during pregnancy, labor/delivery, and postpartum, during lactation, as well as for their infants. The discussion will encompass biological/physiological considerations as well as psychosocial factors that may affect safety and effectiveness of ARV used as treatment or prophylaxis for HIV. We reviewed PubMed and Web of Science for original articles and reviews using the keywords ‘HIV,’ ‘women,’ ‘pregnancy,’ ‘breastfeeding,’ ‘lactation,’ ‘infant,’ ‘prevention of mother to child transmission,’ ‘perinatal transmission,’ ‘antiretroviral,’ “reproductive potential, ‘risks,’ ‘safety,’ for articles published since 2010. In addition we reviewed reference lists of some of the articles, recent conference abstracts and WHO and US HHS guidelines.

2.2. Current antiretroviral therapy recommendations for people with HIV of reproductive potential

The World Health Organization (WHO) and the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents (HHS Panel) have developed recommendations and clinical considerations for the treatment and prevention of HIV Current guidelines recommend ART for all persons with HIV to improve their health and reduce the risk of transmission regardless of CD4 count [26]. These recommendations are based on several clinical trials and observational studies demonstrating an improved rate of virologic suppression and a reduction in morbidity and mortality rates among persons who initiated ART immediately following diagnosis [22,27]. Maintaining a plasma viral load of < 200 copies/mL is critical for reducing the risk of sexual transmission, a concept often recognized as undetectable equals untransmittable (U=U) [26].

Maintaining an undetectable viral load is also critical for reducing risk of perinatal transmission to < 1%. Specifically, when considering an ARV regimen for women/people of reproductive potential, the guidelines recommend that clinicians offer comprehensive reproductive and sexual health counseling and care, as well as consider the regimen’s effectiveness, PK data during pregnancy, interactions with other drugs, teratogenic potential of the drugs, and possible adverse outcomes for pregnant women or their infants [17,26]. Counseling should include discussions of topics such as reproductive desires, maintaining viral suppression to optimize health, safe and effective contraceptive options, and special considerations for ARV use when trying to conceive or during pregnancy [17,26]. A pregnancy test should be performed prior to ART initiation in all women of reproductive potential [26]. In many settings, most people with HIV will be on ARV at the time they conceive.

For pregnant persons, the guidelines recommend ART initiation as early in pregnancy as possible, to decrease the maternal viral load, maintain viral suppression, optimize health outcomes, and minimize the risk of perinatal and sexual transmission [26]. Prior to ART initiation, individuals should be counseled on the benefits and risks associated with use of specific ARV drug regimens during pregnancy to make an informed decision with their healthcare provider. Persons who are receiving fully suppressive ART when they become pregnant are encouraged to continue their regimen throughout pregnancy [26]; indeed, in the majority of cases, no change in ART will be made. However, clinicians should counsel those

receiving ARVs with potential safety concerns or with a risk of virologic instability due to PK changes in pregnancy; this is an unusual scenario that may necessitate an informed decision about whether to continue the current regimen with more frequent monitoring or to switch regimens [17,26].

Recommendations are updated frequently to reflect new evidence for the safety and efficacy of newer ARV regimens, clinical experience, and support for evidence-based, patient centered counseling to make shared decisions. Regarding infant feeding options for PWH, the recommendations are to counsel pregnant women about infant feeding options early in pregnancy, to emphasize the importance of maintaining a suppressed viral load throughout pregnancy and postpartum, and to review infant feeding plans following delivery. In most of the settings with high HIV prevalence worldwide, breastfeeding while the person receives ART is recommended [26,28]. While avoidance of breastfeeding and replacement feeding had been recommended in the United States for PWH, a recent update of the U.S. HHS guidelines supports informed, shared decision making with the breastfeeding parent, and supports breastfeeding, if desired [17], when the mother is adherent to the ARV regimen and has maintained virologic suppression during pregnancy and the breastfeeding period [26]. Breastfeeding confers many health benefits to both the mother and the infant, in both resource-rich as well as resource-limited settings.

2.3. PrEP in women of reproductive potential

Antiretroviral agents are also used as pre-exposure prophylaxis (PrEP) for HIV in people who do not have HIV but may be at increased risk for HIV acquisition [29]. PrEP has been approved for use in gay, bisexual and other MSM, heterosexual women and men, as well as people who inject drugs, and is highly efficacious when taken as prescribed in preventing HIV through sexual activity (99%) and in preventing transmission through injection drug use (at least 74%) [29]. In the initial studies of PrEP among cis-gender women, low adherence and operational issues precluded reliable conclusions about efficacy of preventing sexual acquisition of HIV [30–32]. Subsequent trials with higher medication adherence of oral PrEP provided substantial evidence of efficacy among women [17,33,34].

There are only two agents that are currently FDA-approved for use as PrEP in cis-gender women: oral daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), which provides greater than 90% protection against acquiring HIV [35]; and long acting cabotegravir (CAB-LA), which is given as an intramuscular injection every 2 months and has superior efficacy to TDF/FTC in women [36]. Tenofovir alafenamide (TAF) has not been approved due to non-inclusion of cis-gender women in the initial clinical trials; similarly, on-demand PrEP regimens have not been tested or approved for cis-gender women. Phase III clinical trials studying the efficacy of TAF for cis-gender women are ongoing.

The use of ARV as PrEP will likely impact many more women worldwide. In sub-Saharan Africa, studies have shown that young women have relatively high uptake of oral PrEP, however adherence declines substantially over time as daily pill taking can be challenging [37]. Long-acting PrEP can help to overcome some of these challenges. In the United States, PrEP uptake is increasing, but only about 30% of people who could benefit from PrEP were prescribed it in 2021 [38]. PrEP is especially underutilized by women; only 12% of women

who were eligible for PrEP were prescribed it in 2021 [38]. Cis-gender women may not be aware of PrEP, may not consider themselves at risk of HIV, may feel that the use of PrEP is stigmatizing, or may be concerned about side effects. Other barriers are financial concerns, medical mistrust and privacy concerns [39]. There are some known safety concerns with TDF, for instance, long-term use of TDF by persons with HIV has been associated with risk of renal dysfunction and reduction in bone mineral density [40]. However, in a meta-analysis of 13 randomized clinical trials of PrEP, there was no significant difference in risk of grade 3 or 4 clinical adverse events or serious adverse events between the TDF and control groups and no significant difference in risk of renal or bone adverse events [41]. Long-acting CAB could mitigate adherence challenges, however there is a lack of prospective safety data during pregnancy, which should be discussed with women of reproductive potential. It has a long half-life which is 32% longer in women than in men and 33% longer in persons with elevated body mass index (BMI) [42]. There is also a prolonged PK ‘tail’ among persons with elevated BMI [42]. New modalities are on the horizon that will combine PrEP with hormonal contraception. The dapivirine vaginal ring has shown some efficacy and has been approved by WHO for use in several countries as another prevention choice for women at substantial risk of HIV infection when other PrEP options are not available or acceptable [17,18].

For pregnant women, the normal physiologic alterations of pregnancy (such as increased volume of distribution and changes in renal clearance) can have impacts on ARV pharmacokinetics, with implications for PrEP dosing and adherence monitoring [43]. For PrEP monitoring, the dried blood spot test measuring tenofovir diphosphate (TFV-DP), an intracellular metabolite of tenofovir, is an objective, well-validated and commercially available method for monitoring adherence to TDF-based PrEP regimens [44]. However, TFV-DP concentrations have been found to be nearly one-third lower among women in pregnancy compared to women in the post-partum period, even with near-perfect PrEP adherence [43]. In light of these pharmacokinetic differences, United States guidelines recommend that pregnant and postpartum women starting oral PrEP use additional HIV prevention strategies for at least 20 days after PrEP initiation, to maximize protection until PrEP steady state levels are reached [17]. Additional considerations for TDF in pregnancy are reviewed below (see 3.2 Pharmacokinetic variations of ARV in pregnant and lactating women). For other PrEP modalities, the terminal phase half-life of long acting cabotegravir (CAB-LA) appeared similar between pregnant and nonpregnant women, though data are limited [45].

Although available data are reassuring, knowledge gaps remain regarding the safety and outcomes of PrEP during pregnancy and breastfeeding. As of 2020, only five studies reporting on oral PrEP’s safety and outcomes during pregnancy and breastfeeding had been completed, and another nine were ongoing or planned (Table 1) [46]. For the long-term dapivirine ring, a randomized controlled trial comparing the safety of the dapivirine vaginal ring and oral TDF/FTC for PrEP in the third trimester among pregnant women in sub-Saharan Africa demonstrated that pregnancy complications among both PrEP modalities were rare and comparable to the background rate of the local populations [52]. A sub-study of a different randomized controlled trial evaluating the safety and efficacy of the dapivirine ring compared to placebo in non-pregnant women showed that periconceptional exposure

to dapivirine ring was not associated with differences in maternal, pregnancy, or infant outcomes [53]. As studies of injectable CAB-LA in cisgender women required effective contraception for women to participate, data on its associated pregnancy-related outcomes are still scarce [56].

Persisting individual, community, and structural-level challenges affecting uptake and adherence limit the real-world effectiveness of PrEP as an HIV prevention strategy among women of reproductive potential [57]. A survey of U.S. women showed that PrEP stigma, particularly fears of being considered promiscuous or HIV positive and expected disapproval from partners, family, and peers limited PrEP interest [58]. In an international PrEP delivery study for at-risk pregnant and post-partum women in a region with high HIV prevalence, only 22% initiated PrEP and 39% of these women continued to use PrEP after the first month, with side effects and no perceived HIV risk cited as common reasons for discontinuation [59]. Otherwise, concerns about the safety of PrEP medications themselves; negative perceptions of PrEP among partners, peers, or the broader community; challenges of adhering to daily regimens; and fears of being mistaken for having HIV may influence PrEP adherence [60]. More discrete long-acting PrEP modalities, such as dapivirine and CAB-LA, hold promise in mitigating many of these stigma- and adherence-related challenges associated with oral PrEP. CAB-LA was found to be superior to oral TDF-FTC, due largely to its adherence advantage [36]. Novel combined modalities pairing PrEP with other preventive medications for women may confer similar advantages. For example, work is currently ongoing on combining PrEP with hormonal contraception in multi-prevention technologies that could be given vaginally, orally, or parenterally.

3. Challenges of antiretroviral therapy in people with HIV of reproductive potential

3.1. Access to healthcare and systems barriers

Adherence to one’s ARV regimen is critical to maintaining viral suppression, preventing transmission to others, and avoiding drug resistance. However, women of childbearing potential often face constraints that affect their access and continuation of HIV treatment and care. In 2004, the WHO released a policy statement acknowledging the inequalities affecting women’s access to and interaction with HIV prevention and care service systems [61,62]. Multiple studies have found that women often had lower ART adherence than their male counterparts [26,61]. Clinical, psychological, cultural, and social aspects, particularly relevant to women of childbearing potential, have been shown as possible barriers to accessing and maintaining optimal adherence to treatment. Barriers disproportionately affecting women include restricted access to health care due to transportation barriers, less knowledge of ART options, and specific reproductive health concerns. Additional factors include side effects, HIV stigma, work-related demands, social relationships, expectations and pressures, religious beliefs, and women’s perception of risks [61,63,64]. Addressing these constraints is important to improving women’s access and adherence to ART.

Many studies have also identified weaknesses in health systems resulting in fragmented care of women receiving ART, particularly in lower-resourced settings. For example, prenatal

care, STI care, primary care, TB care, pediatric care, etc. may be offered in different healthcare settings that may not communicate with each other, making adherence more challenging. Inconsistent adherence to ART was often the result of scheduling difficulties, such as long wait times and overbooked appointments, as well as poor follow-up tracking [65]. These factors may be exacerbated by resource constraints, such as human resource shortages, high staff turnover, and supply shortages [65]. Additionally, the lack of provider knowledge on reproductive care, contraception options, or drug interactions with ART, and lack of training on current treatment protocols and procedures may limit the ability of healthcare workers to provide optimal reproductive, maternal and HIV care [65]. In light of these barriers, community-based models and technological strategies have been leveraged to strengthen ART service delivery and improve adherence [66,67].

Interactions between women of reproductive potential and healthcare providers are also a factor affecting women's engagement in care. Stigmatizing perceptions toward women of reproductive potential with HIV affects the quality of care and engagement provided. This is an issue for both resource-limited as well as resource-rich settings. The perceptions among healthcare workers relating to HIV-related stigma may lead to ineffective care and treatment, as well as a lack of trust between patient and provider. Fears of confidentiality breaches and social discrimination were frequently reported by women who have experienced negative or stigmatizing attitudes from their health care provider [65]. These barriers highlight the inefficiencies of health systems in successfully caring for and supporting women of reproductive potential with HIV. Addressing these health systems barriers needs to be a priority to ensure adherence to ARV regimens, continued engagement in care, and overall health among women of reproductive potential.

3.2. Pharmacokinetic variations of ARV in pregnant and lactating women

Of the estimated one million pregnant women with HIV globally, 85% received ART in 2019 [68]. Maintaining adequate drug exposure throughout pregnancy and breastfeeding decreases the risk of viral rebound, perinatal transmission, and complications of uncontrolled HIV infection [69]. However, during pregnancy, women experience an array of physiologic changes that may affect ARV exposure. Changes in drug absorption, distribution, and metabolizing enzymes may impact ARV drug concentrations leading to variations in drug response [70]. Nevertheless, our knowledge of the PK and safety of new pharmacologic agents in pregnancy is often inadequate. Many published studies addressing PK differences in women are small, retrospective in design, and evaluated only a few parameters [71]. Women, especially pregnant and lactating women, have historically been underrepresented in PK and clinical trials, as pregnancy is often an exclusion criterion for many studies, particularly early phase drug trials, and women who become pregnant during the study period are often encouraged to discontinue their participation [68]. This lack of inclusion has contributed to the delayed availability of clinical and PK and safety data of ARV agents during pregnancy. This issue has received recent attention – in 2018, the FDA published guidance to facilitate the inclusion of pregnant and lactating women in clinical trials, considering both ethical and scientific factors and a risk-benefits assessment [72]. Additionally, the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

(IMPAACT) has led dedicated studies on pharmacokinetic properties of antiretroviral drugs during pregnancy and postpartum (IMPAACT P1026s; IMPAACT 2026, enrolling) [73,74].

There is also a need to assess fetal and infant drug exposure during pregnancy and breastfeeding. ARV use during breastfeeding has been shown to significantly reduce the risk of HIV transmission. However, there are limited studies that focus on drug-related toxicities and drug resistance in breastfed infants exposed to ARV [70]. Clinical and PK studies of ARVs should be designed to include pregnant and lactating women in phase 3 or earlier trials to understand the effects of these regimens on drug exposure, transmission, and pregnancy outcomes, using appropriate safety standards for research inclusion [68,75]. Physiologically based models have shown success in predicting maternal-fetal drug pharmacokinetics for certain ARVs [76,77]; however, more clinical validation for such modeling approaches is needed.

Certain pharmacologic factors should be considered when initiating or adjusting ARV in women who are or who may become pregnant. For example, even among preferred ARV regimens during pregnancy, adherence may be more challenging for drugs requiring more than daily dosing, such as raltegravir (RAL), compared with daily dosing ARVs. Other ARVs, such as NVP, have an increased risk of serious adverse events in women in general (such as hepatotoxicity and life-threatening hypersensitivity reactions), for which some studies have demonstrated an even higher risk during pregnancy [17]. Lastly, variations in ART efficacy may exist, even among preferred ARV regimens [78].

Physiologic changes in the second and third trimesters (increased volume of distribution, increased renal clearance) can affect the PKs of some ARVs and cause plasma concentrations to decrease; concentrations usually return to normal around 6–12 weeks postpartum [79]. As such, modifications to ARV dosing or frequency may be required during pregnancy to ensure target concentrations are achieved [79]. Of note, pharmacokinetic studies to date (ex. IMPAACT 1026) have not found viral load suppression to be affected by many of the pharmacokinetic changes in pregnancy, though these studies were not sufficiently powered to evaluate viral load suppression. There are consequently no firm guidelines around dose increases for ARVs during pregnancy. Given ongoing uncertainties about the potential impact of lower pharmacokinetic levels, clinicians may consider more frequent viral load monitoring during pregnancy if concerns arise.

Pharmacokinetic studies of TDF-based ART have found that women have lower plasma concentrations and increased clearance of tenofovir (TFV) in the second and third trimesters compared to the postpartum period [80,81]. However, the clinical implications of lower TFV concentrations in pregnancy remain unknown. Inverse correlations between body weight and tenofovir concentrations have been found for women in the third trimester and postpartum [81], leading some to suggest more frequent therapeutic drug-level monitoring for women on TDF who are obese and pregnant [81].

Cobicistat-boosted regimens are generally discouraged for use in pregnant women due to the potential of reduced ARV concentrations, an effect not observed in non-pregnant women [82]. However, changes in ARV regimens during pregnancy can be associated with

challenges with adherence and a potential risk of drug resistance, perinatal transmission, and other adverse outcomes. Therefore, it is recommended that women on well-tolerated pre-pregnancy ARV regimens with sustained viral suppression continue on their regimen throughout pregnancy [17]. People presenting on ARVs with high risk for toxicity during pregnancy may need to be transitioned to other recommended ARV regimens. In other instances, such as in pregnant women with sustained viral suppression on regimens with potentially increased risk of virologic failure during pregnancy (ex., cobicistat-boosted regimens) or insufficient dosing or safety data (such as oral two-drug regimens, or long-acting injectables), the decision to continue the current regimen or switch to a recommended ARV regimen should be made on a case-by-case basis, with shared, informed decision-making between patient and provider. In these situations, more frequent viral load monitoring (every one to two months) may be needed if pre-pregnancy regimens are continued [17]. In some other settings, however, viral load monitoring may not be readily available.

3.3. Interactions of ART with hormonal contraceptives

Hormonal contraceptives (which include methods containing estrogen plus progestin or progestin alone) are used by over 20% of women not actively seeking pregnancy [83]. Concerns relating to the co-administration of ART with hormonal contraceptives exist due to potential interactions that may influence drug effectiveness. Specifically, interactions between specific ARV drugs and certain hormonal contraceptives may alter either or both ARV or contraceptive drug concentrations. This could potentially lead to reduced contraceptive efficacy, increased hormone levels leading to adverse events [84], increased ARV toxicity, or subtherapeutic ARV levels, with associated risks of HIV transmission, drug resistance and adverse HIV-related outcomes. However, most ARVs used for treatment or prevention have limited interactions with hormonal contraceptives, with the exception of efavirenz (EFV) [26]. Thus, unless an ARV regimen has a known significant interaction with the hormonal contraceptive being considered, concerns about potential drug-drug interactions should not preclude offering hormonal contraceptives for PWH [26,85,86].

The cytochrome P450 system contains the key enzymes to metabolize the contraceptive steroid hormones, ethinyl estradiol and progestogens [87]. Some antiretroviral drugs are also metabolized by these cytochromes, and some can inhibit or induce some cytochrome isoenzymes influencing the effectiveness of certain hormonal contraceptives. For example, cobicistat is an inhibitor of the cytochrome P450 3A system [84]. ARV regimens containing PIs and NNRTIs can also induce or inhibit the enzymes in the cytochrome P450 3A system affecting hormone concentrations and contraceptive efficacy [87]. In contrast, ARV regimens containing NRTIs and INSTIs have been found to have no effect on the hormone metabolizing enzymes [88].

The risk of interaction depends on both the specific ARV drug (or drugs) and the specific hormonal contraceptive modality being considered [86]. ARV drugs associated with known significant changes in hormonal contraceptive concentrations include efavirenz (EFV) (decreases progestin concentrations, affecting the efficacy of both progestin-only (including implantable) and combined estrogen-progestin contraceptives) [26,86]. Particularly,

significant interactions were found between EFV with combined oral contraceptive pills and with levonorgestrel or etonogestrel subdermal implants [84,89,90]; whereas depot medroxyprogesterone acetate (DMPA) is not affected. Other ARVs with known impacts on hormonal contraceptives include cobicistat- or ritonavir-boosted regimens, which are associated with an increased risk of hyperkalemia when used with drosperinone-containing contraceptives. Elvitegravir/cobicistat (EVG/c) and boosted protease inhibitors decrease ethinyl estradiol levels [86] and increase progestin exposure, leading to the potential of intermenstrual bleeding for combination contraceptives and the potential of progestin-related adverse effects for progestin-only contraceptives [26]. Boosted-PI ARV regimens may decrease the efficacy of hormonal methods for women with HIV [86,91]. In general, however, PK interactions of DMPA or intrauterine systems with ARVs do not appear to be significant, although further study is needed. Additionally, no evidence suggests that hormonal contraceptives alter the PK of ARV regimens containing NRTIs, NNRTIs, or PIs. One exception is fosamprenavir, a PI prodrug for which the risks of concomitant combination hormonal contraceptives are considered to outweigh the benefits, due to concerns of decreased ART effectiveness [86]. PK studies of the NNRTIs NVP and EFV demonstrated no changes in ART concentration between women using hormonal contraceptives and those not [86]. As more women with HIV of reproductive potential are using hormonal contraceptives, additional studies evaluating the PK interactions of ARVs and hormonal contraceptives as well clinical studies are needed to assess changes in drug efficacy, ovulation, and pregnancy outcomes. Of note, some contraceptive options may also interact with antimicrobials used to treat tuberculosis, often a coexisting infection in people with HIV, particularly in resource-limited settings [92,93].

3.4. Monitoring ARV safety during pregnancy and lactation

As new ARV regimens are approved and recommended for women of reproductive potential, surveillance systems are needed to evaluate their safety and efficacy, especially for use during the pregnancy and lactation periods. Existing safety data sources may include cohort and surveillance studies, registries, clinical studies, and electronic health record databases. However, many active sources are fragmented and limited in available data resulting in difficulties evaluating potential risks associated with ART in women and their infants. Large numbers of exposures are required to observe differences in rare adverse maternal and fetal outcomes [94]. The Botswana Tsepamo birth defects surveillance study was one of the first to collect sufficient prospective exposures. The Tsepamo study initially reported a 0.94% risk of NTDs in 494 periconception DTG exposures in comparison to 0.12% in non-DTG exposures [95]. Based on the initial findings from this study, WHO and the U.S. HHS Panel released recommendations against the use of DTG in ARV regimens for women of reproductive potential [26,96]. Continued surveillance from the Tsepamo study reported a lower NTD risk of 0.11% with periconception DTG use, which was not significantly elevated compared to the NTD risk of other ARV drugs used in pregnancy [97]. Studies from other settings, included Brazil [98] and the U.S [99], have since confirmed the lack of an association between DTG and NTDs. The updated findings encouraged the U.S. HHS Panel to revise their guidance and support the use of DTG in ARV regimens for women of reproductive potential, while also directing attention to the need for time efficient and reliable pharmacosurveillance data. Prospective surveillance systems

of prenatal pharmacologic exposures are critically needed, including in the United States [100]. Electronic health record systems may be the solution in the long term, however there are currently many obstacles to their use, including lack of interoperability and limited ability to link mother and child records. More recently, an algorithm has been developed to be used with medical claims data, that can detect periconceptional exposures and infant outcomes, including rare outcomes such as NTD [99,101]. In the absence of prospective surveillance, this use of medical claims data functions in almost real-time as a method of pharmacovigilance. Another approach is the Antiretroviral Pregnancy Registry (APR), a prospective international registry established in 1989 to monitor prenatal ARV exposure and detect pregnancy outcomes that may be associated with such exposures [102]. However, a registry is a passive form of surveillance and as a result it has been underpowered to detect signals in a timely fashion. For example, as of 31 January 2023, there were 873 first trimester DTG exposures reported to the APR, but 2,000 exposures are required to detect a signal for events as rare as NTD [103]. Additional studies reporting on the safety and efficacy of ARVs in women of reproductive potential include the Pediatric HIV/AIDS Cohort Study's Surveillance Monitoring of ART Toxicities (SMARTT) [104], the European Collaborative Study (ECS) [105], and the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (P1026s/IMPAACT 2026) [106]; all these cohorts are useful but may be underpowered to detect rare outcomes.

Challenges remain to sufficiently assess the safety and efficacy of ART in women of reproductive potential. Guidance is limited for standardizing definitions and data collection tools to measure relevant pregnancy outcomes. Developing standardized exposure and outcome definitions can improve the understanding and comparison of outcome rates globally [107]. The lack of relevant training and incentives for providers and health care staff to report often leads to data quality issues, such as reporting bias, under-reporting in voluntary registries, such as the APR, and incomplete or inaccurate data. Frequent training for health care workers are necessary to ensure events are recorded accurately and completely and to encourage reporting to registries.

4. Risks of ARV in women of reproductive potential

4.1. Maternal health outcomes

ART has had a profound impact on reducing HIV-associated morbidity, mortality, and perinatal and sexual transmission, effectively changing HIV from a life-threatening illness to a manageable chronic disease [108]. However, improvements in HIV mortality have been coupled with an increasing awareness of toxicities associated with long-term ART use. These include an increased risk of chronic diseases such as osteoporosis, metabolic syndrome, and cardiovascular disease [109–112].

ART's effects on maternal health in pregnancy often mirror effects seen in non-pregnant adults [113]. However, studies have found increased risk for some conditions specific to pregnant women on ART. INSTIs are associated with more weight gain than other classes of ARVs; DTG/TAF-containing regimens, in particular, had higher weight gain during pregnancy, compared to other regimens [106]. TAF has been associated with more weight gain, compared to TDF [114]. In addition, a higher prevalence of gestational

diabetes has been seen among women with certain PI-based regimens [113,115], and DTG-associated pre-pregnancy obesity may increase the risk for gestational diabetes [116]. In other instances, some ARV drugs have overlapping side effect profiles with symptoms or conditions for which pregnant women (or pregnant women with HIV specifically) have an increased risk. For example, use of EFV versus other ARVs has been associated with an increased risk of depression or suicidal thoughts, which are more common among pregnant women with HIV overall [113]. Similarly, while women have an increased risk profile for certain hepatic disorders in pregnancy, PI-based regimens may also increase the risk of elevated liver-enzyme levels in pregnant women with HIV [117]. Of note, while some observational studies have found differences in association with hypertension between certain ARV regimens [26] or associations of ART and pre-eclampsia [118], meta-analyses have reported conflicting evidence on potential associations between ART and hypertensive disorders of pregnancy [119,120]. Compared to pregnant women without HIV, US women with HIV and on ART have more frequent chronic comorbid conditions (psychiatric, pulmonary, cardiovascular, hematologic and neurologic), but not more obstetrical complications [121]. Screening and treatment for chronic conditions prior to and during pregnancy is essential.

4.2. Birth and fetal outcomes

While there have been concerns about possible adverse effects of prenatal ARV exposure on birth defects and adverse birth and fetal outcomes, there is inconsistent evidence regarding the effects of specific ARV drugs and drug classes. Factors that may contribute to the potential harm of the fetus from ARV exposure include gestational age at exposure, the duration of ARV exposure, drug dosage, drug interactions, and other maternal comorbidities [17]. However, limitations in study design have made it challenging to establish a causal link between specific ARV drugs and rare adverse outcomes. These challenges include low numbers of reported exposures, inappropriate comparison groups, an inability to stratify findings by timing of ART use, and the lack of robust post-marketing surveillance systems for pregnant women taking ARVs in the United States [17]. Despite these issues, multiple observational studies to date have found no difference in rates of all birth defects between first-trimester ARV drug exposures and later term exposures, though less data are available for newer ARV drugs that are now recommended for pregnant women [17]. Recently evolving guidance surrounding the use of DTG in pregnant women with HIV (as reviewed in Section 3.4) serves as an illustrative example of the challenges of identifying associations between ARV drugs and fetal or birth outcomes.

Data evaluating associations between ARV drugs and pregnancy loss prior to 20 weeks of gestation are limited, as many early pregnancy losses are undetected or underreported. An analysis of Marketscan and Medicaid data found women with DTG exposure during pregnancy have a slightly increased risk of early pregnancy loss, compared with women exposed to other ARV drugs [99]. The Women's Interagency HIV Study (WIHS) and the PROMISE trial reported conflicting evidence related to early pregnancy loss with PI-based ART, with the former study reporting lower rates of early pregnancy loss compared with exposure to NRTIs or no ART [122], but the latter study reporting a higher risk of early

pregnancy loss [122,123]. Whether there is an effect of the timing of ART initiation on early pregnancy loss is still unknown.

Rates of stillbirth (≥20 weeks gestation) range from 0.5% to 11.4% in women with HIV [17], which may be higher than in women without HIV, although the evidence is not conclusive. The relationship between stillbirth and specific ARV regimens is unclear, as studies evaluating this outcome are limited. One study found periconceptional use of TDF-based ART to be associated with a reduced risk of stillbirth compared to other regimens [124]. A comparison of TDF-based and ZDV-based ART, as well as EFV-based and NVP-based ART, found no significant differences in rates of stillbirth [125]. Similarly, a randomized controlled trial reported that the rate of stillbirth in pregnant women receiving DTG-based ART was not significantly higher than that in women on EFV-based ART or other ARV regimens [99,106]. A national US cohort study found no increased rate of stillbirth among pregnant women with HIV and periconceptional exposure to ARVs compared to the general population [99].

More studies have assessed the relationship of periconception ART on birth/neonatal outcomes such as preterm birth, small for gestational age, and low birth weight. These studies have shown possible associations between preterm birth (delivery before 37 weeks) and maternal ART, though the risk varies according to the drug regimen used. Women receiving ZDV-based maternal ART had a reduced risk of preterm birth [17]. In contrast, observational studies comparing maternal ARV regimens that include boosted PIs showed there may be a correlation between ritonavir (RTV) and an increased risk of preterm birth, particularly with lopinavir (LPV)-containing regimens [126–129]. The timing of ART initiation may also influence risk of preterm birth, as studies have reported women who initiate ART before pregnancy have an increased risk of preterm birth as compared to women who initiate ART during pregnancy, particularly after the first trimester [17]. Infant growth restriction is also not uncommon in children born to women with HIV, however, results from studies exploring the effect of maternal ART on this outcome are mixed. In infants exposed to maternal ART, the rates of low birth weight have ranged from 8.9% to 23.8%, and the rates of small for gestational age have ranged from 7.3% to 31% [17]. Studies comparing the effects of ZDV single drug therapy, NNRTI-, and PI-based regimens, showed there may be an association between NNRTI- and PI-based regimens and an increased risk of low birth weight infants [130]. Women prescribed PI-based regimens were also at an increased risk of delivering small for gestational age infants [126]. Additional studies are needed to establish whether there are causal links between specific maternal ARV regimens and pregnancy outcomes. Women who initiated ART prior to pregnancy have been found to have increased placental dysfunction from vascular malperfusion, compared with women on ART before conception, a finding which was significantly associated with poorer outcomes including pre-term birth and low-birth weight [131]. Although some ARVs have been associated with a potential risk of adverse fetal and birth outcomes, the benefits of ART use in pregnant women and in preventing transmission of HIV to the infant generally outweigh the risks.

5. Conclusions and expert opinion

ART has dramatically changed the landscape by prolonging and improving the quality of life for PWH. Notably, for women with HIV, ART supports reproductive autonomy including plans to prevent pregnancy and to have children. ART has resulted in improvements across a range of health outcomes, including reproductive and birth outcomes. By improving their general health, more women with HIV have been able to achieve and maintain pregnancy and deliver healthy babies. In addition, ART has drastically reduced the risk of perinatal transmission of HIV to 1% or less, when it is taken with good adherence during pregnancy, labor and delivery, and during breastfeeding. Furthermore, ARV agents used as PrEP have the potential to be used by many more women who do not have HIV but are at risk of acquiring HIV.

Even though ARV use has increased worldwide, with its benefits well documented, some challenges and risks are associated with its use among women of reproductive potential. Such challenges range from difficulties in access, still encountered in many settings worldwide, to challenges maintaining good adherence, which is critical to achieve the intended goals. Lack of awareness of PrEP options for HIV and of recognition of women's own risks for HIV remains an issue even in the United States. Furthermore, many studies across a variety of settings have shown challenges with adherence with daily oral PrEP among healthy young women. For PWH, it is well documented that the postpartum period is a time when adherence may be particularly challenging.

While the currently approved ARV agents are generally safe, there are particular considerations when used in pregnant or in lactating women. Physiologic changes in pregnancy may result in differences in metabolism of particular ARVs, which may result in decreased exposures leading to inadequate viral suppression or the need for more frequent dosing which may present additional adherence challenges. Prenatal exposures also have the potential to adversely affect the developing fetus. Given that pregnant and lactating women have historically been excluded from research studies, particularly early phase drug development studies, our knowledge of the potential adverse effects of newer agents on the fetus is often inadequate or based on animal studies or individual case reports, which may not be representative of the real risks. An example of that was the case of EFV, which was associated with NTD in some animal studies, with resultant reluctance to use it among women of reproductive potential at a time when there were few good ARV options to achieve viral suppression. This risk was not demonstrated in humans after a larger number of exposures and EFV was later included in the preferred regimens, but this was not until after a decade of underutilization of a potentially effective ARV option. Additionally, most contraceptive methods are safe for use by women with HIV who desire to prevent pregnancy. Potential drug interactions between certain hormonal contraceptives and ARVs need further study. As pregnant people may need treatment for other conditions, such as hypertension or gestational diabetes, and many may also need treatment for tuberculosis or other infections, the potential of drug interactions between ARV and other drug classes may additionally complicate treatment and make adherence more challenging.

A current challenge is the lack of prospective, systematic surveillance of the effects of prenatal exposures in the U.S. or in some other settings. Existing registries have several drawbacks, including incomplete data resulting in significant lag in collecting information on an adequate number of exposures; and current surveillance systems also have challenges with timeliness and completeness of their data. Timely and comprehensive population-based systems are needed to have thorough pharmacovigilance for newer ARV agents, which is critical in assuring their safety for mothers and infants.

6. Five-year plan

Great progress has been made, but challenges remain. The most important research directions in this field in the next five years will be the development of even longer acting ARV (currently ARV agents that are administered every 6 months are being evaluated in advanced stage clinical trials). Such long-acting agents could be instrumental in decreasing adherence barriers and further improving quality of life for women with HIV. However, monitoring for the safety of newer agents, particularly in new drug classes, including safety for infants, will be paramount. Innovative data science can take advantage of medical claims data as a means for post-marketing drug safety surveillance. However, truly interoperable systems of electronic health records that can link maternal and child records and capture pregnancy and other medical information completely may hold the key to such a comprehensive system in the future. Development of multi-purpose technologies (combination PrEP and contraception (including long-acting), or PrEP and other STI prevention) as well as innovative methods of delivery of ARV, including long-acting ARV (such as through microneedle patches or other methods) may help in improving adherence and de-medicalizing HIV prevention. Additional ways to deliver pre- or post-exposure prophylaxis (PrEP or PEP) in women (shorter, easier to administer regimens timed around the time of exposure) will help advance our preventive armamentarium. Finally, even though likely not in the next five years, the future of antiretroviral therapy may not be in small molecules but (at least in part) in antibodies, immune activation modifiers or gene editing technologies; a substantial amount of ongoing work is demonstrating incremental progress which may shape a very different future for people with HIV. There will be a need to increase the number of women enrolled in clinical research trials with enhanced support, as needed, especially for the studies involving such newer technologies, so that the disparities of the past are not perpetuated for women.

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Article highlights

- Antiretroviral therapy (ART) has greatly improved the quality of life for people with HIV, including women of reproductive potential, by supporting reproductive autonomy and leading to better health outcomes.
- ART has substantially reduced the risk of perinatal transmission of HIV when taken with good adherence during pregnancy, labor, delivery, and breastfeeding. However, challenges and risks are associated with ART use among women of reproductive potential, including difficulties in access, maintaining good adherence, and lack of awareness of PrEP options.
- Prenatal exposures also have the potential to adversely affect the developing fetus, and our knowledge of the potential adverse effects of newer agents on the fetus is often inadequate.
- Most contraceptive methods are safe for use by women with HIV who desire to prevent pregnancy, but potential drug interactions between certain hormonal contraceptives and ARVs need further study.
- There is a current challenge in the lack of systematic surveillance of the effects of prenatal exposures, and comprehensive population-based systems are needed for thorough pharmacovigilance of newer ARV agents.

Table 1.

Studies reporting on maternal and infant outcomes with oral daily or long-acting PrEP exposure during pregnancy and breastfeeding.

Study; Study Location; Lead author; Year	PrEP regimen	Design & Population	Designed for pregnant women?	PrEP-exposed pregnancies; time exposed	Pregnancy outcomes	Infant outcomes
Oral daily PrEP[a] [46]						
Partners PrEP Study; Kenya and Uganda; Mugo; 2014 [47]	Daily TDF[b] vs. TDF-FTC[c] vs. placebo	Randomized, double-blind, placebo-controlled trial (Phase 3) in serodiscordant couples. 1785 women enrolled; 431 total pregnancies occurred	No; safety of periconceptional PrEP in HIV uninfected women was a secondary objective.	n = 335; Median duration of gestation at time of pregnancy detection: TDF 37 days (IQR 29–46) TDF-FTC: 35 days (IQR 29–42) Pregnancy tests performed at enrollment and monthly, and if positive, study product withheld.	No difference in pregnancy loss (31% in PrEP exposed vs. 32% in placebo; p = 0.46) or preterm birth (3.4% in PrEP exposed vs. 7.7% in placebo; p = 0.16)	Congenital anomalies: no difference (any TDF: 5%; placebo 7.6%; p = 0.51). Growth at 1-year: no difference in z-scores for head circumference, length, or weight
FEM-PrEP; Kenya, South Africa and Kenya; Callahan; 2015 [48]	TDF-FTC vs. placebo	Randomized, double-blind placebo-controlled trial. 2120 women enrolled; 115 pregnancies with available outcome data occurred.	No	n = 69 Pregnancy tests were performed monthly and, if positive, study product was withheld	No difference between study arms (data by arm not reported) among pregnant women with outcome data (30/115)	None reported
MTN-003/VOICE; Uganda, South Africa and Zimbabwe; Bunge; 2015 [32]	TDF vs. placebo; TDF-FTC vs placebo; 1% TFV[d] vaginal gel vs placebo	Randomized placebo-controlled trial. 5029 women enrolled; 452 total pregnancies occurred.	No	n = 263; Pregnancy tests were performed monthly and, if positive, study product was withheld	Early pregnancy loss was not higher among women exposed to TDF-containing PrEP compared to placebo	None reported
Partners Demonstration Project; Kenya and Uganda; Heffron; 2018 [49]	Tenofovir-based PrEP vs. placebo	Open-label demonstration project in serodiscordant couples. 1013 women enrolled; 126 total pregnancies occurred. PrEP-exposed pregnancies were compared with pregnancies from placebo arm of Partners PrEP Study.	No; Pregnancy tests conducted at screening visit and as clinically indicated thereafter. If positive, PrEP continuation throughout pregnancy was offered.	n = 30; Women dispensed PrEP a median of six months (IQR 4–8) during pregnancy; 52% of women took at least 80% of expected doses.	No difference in pregnancy loss (17% in PrEP-exposed vs. 24% in control; p = 0.7) or preterm birth (0% vs. 8%; p = 0.4) by PrEP use in pregnancy	Length: PrEP exposed infants lower z-score at 1-month; no difference at 1-year
PriYA Programme; Kenya; Dettinger; 2018 [50,51]	Tenofovir-based PrEP	Implementation program; 4680 pregnancies included in safety evaluation	Yes	n = 246; 47% initiated PrEP in the second trimester; 41% reported using PrEP for 1-three months during pregnancy	Rates of reported preterm birth were similar between the two groups (3.1% PrEP exposed, 4.2% non-PrEP, p = 0.50), and birthweight (median 3.3 kg in both groups, p = 0.14).	Small for gestational age: no difference (1.9% vs 6.7%, p = 0.18). Congenital malformations: no difference (n = 0 in PrEP exposed vs.13 reported in PrEP unexposed). Weight-for-age, length-for-age, weight-for-length z-scores: no differences (p = 0.60, 0.13, 0.76 respectively).

Study; Study Location; Lead author; Year	PrEP regimen	Design & Population	Designed for pregnant women?	PrEP-exposed pregnancies; time exposed	Pregnancy outcomes	Infant outcomes
Long-acting PrEP						
MTN-042/DELIVER; Malawi, South Africa, Uganda, Zimbabwe; Bungel 2024 [52]	Dapivirine vaginal ring (DVR) vs. TDF-FTC	Randomized, open-label trial (Phase 3); 307 women enrolled (all pregnant)	Yes	150 participants initiated PrEP between 36 and 37 weeks gestation (cohort 1); 157 participants initiated between 30 and 35 weeks gestation (cohort 2). Both cohorts continued until delivery or 41 weeks gestation.	Maternal safety: DVR comparable to TDF/FTC; no SAEs were determined related to study product. Pregnancy complications rare and comparable to local background frequencies.	Median birthweight: 3.2 kg (cohort 1); 3.1 kg (cohort 2). Serious adverse events: 5% DVR, 2% TDF/FTC (cohort 1); 9% DVR, 2% TDF/FTC (cohort 2). Congenital abnormalities: 2% DVR, 4% TDF/FTC (cohort 1); 7% DVR, 6% TDF/FTC (cohort 2).
ASPIRE; Malawi, South Africa, Uganda, Zimbabwe; Makanani; 2018 [53,54]	DVR vs. placebo	Randomized, double-blind, placebo controlled trial (Phase 3). 2629 women enrolled; 179 total pregnancies occurred.	No Pregnancy tests performed monthly and, if positive, study product was withheld	N = 86; median gestational age at pregnancy detection 5.4 weeks (IQR 4.3, 6.8)	No differences in distribution of pregnancy outcomes by study arm.	Congenital anomalies: no difference in overall prevalence between study arms. Infant growth: no differences in infant weight, length, or head circumference by study arm.
HPTN 077; Brazil, Malawi, South Africa, United States; Landovitz 2018 [55]	CAB-LA vs. placebo	Randomized placebo-controlled trial (Phase 2a); 132 women enrolled; 3 total pregnancies occurred.	No Pregnancy tests performed at each visit (screening, enrollment, weeks 2 and 4, injection visits, final endpoint visit) and quarterly follow-up visits. Study product discontinued if positive.	N = 1; pregnancy occurred during tail-phase of study, 8 months after final PrEP dose	Complicated by preeclampsia; early-term delivery	Healthy infant, no birth defects
HPTN 084; Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe; Delany-Moretlwe; 2022 [36]	CAB-LA vs. TDF-FTC	Phase 3 randomized, double-blind trial. 3224 women enrolled; 49 total confirmed pregnancies occurred.	No Pregnancy tests at each visit (screening, enrollment, weeks 2 and 4, injection visits, final endpoint visit). CAB-LA withheld and participant transitioned to TDF-FTC for the duration of pregnancy and breastfeeding if positive.	CAB-LA: N = 29 (1.5 per 100 person-years, confidence interval [CI] 0.9–1.7); TDF-FTC: N = 20 (1.0 per 100 person-years, CI 1–2.2) (data for 31 available at time of data lock) Pregnancy tests at each visit (screening, enrollment, weeks 2 and 4, injection visits, final endpoint visit). CAB-LA withheld and participant transitioned to TDF-FTC for the duration of pregnancy[a] and breastfeeding if positive.	Livebirths: CAB-LA 13/18; TDF-FTC 10/13	Congenital anomalies: none observed

[a] Oral PrEP section adapted from [46].

[b] TDF: oral tenofovir disoproxil fumarate.

[c] TDF-FTC: oral tenofovir disoproxil fumarate-emtricitabine.

[d] TFV: tenofovir.

[e] CAB-LA: long-acting injectable cabotegravir.