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Where are the pregnant and breastfeeding women in new pre-exposure prophylaxis trials? The imperative to overcome the evidence gap

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Abstract

Pregnant and breastfeeding populations are at substantial risk of acquiring HIV in some settings, yet are underrepresented in clinical trials of new pre-exposure prophylaxis (PrEP) agents. Several PrEP formulations are in development (eg, vaginal rings, long-acting injectables, and other modalities). Pregnant and breastfeeding populations are typically excluded from initial clinical trials. We identified 14 PrEP trials of novel agents in non-pregnant or non-breastfeeding

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DLJD searched the literature, contributed to the first draft, review, and editing feedback from other authors, and approved the final manuscript. L-GB reviewed the first draft outline, reviewed and edited the drafts, and approved the final manuscript. EAB, BHC, SD-M, AG, ADL, LS-C, LMN, NM, NMM, LM, and CS reviewed the first draft of the proposal, revised various drafts, and approved the final manuscript. JP conceptualised the idea for the manuscript, revised the first draft, reviewed and edited feedback from other authors, and approved the final manuscript.

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populations, and six phase 1–3 trials and open label extensions among pregnant and breastfeeding populations, that are currently ongoing or complete. A framework shift is needed to consider the ethical costs of excluding pregnant and breastfeeding populations at risk for HIV in PrEP clinical trials and promote inclusion to maximise the benefits from PrEP tools in the pipeline. Research on new PrEP agents should include pregnant and breastfeeding populations to avoid delays in reaching those who could benefit from PrEP after efficacy is established.

Introduction

Over half of HIV infections globally occur among cisgender women (women who are assigned female at birth and identify as girls or women).[1] High HIV incidence among young (ie, 15–30 years old) African cisgender women persists during pregnancy and post partum,[1] and there is evidence that HIV acquisition risk more than doubles during this period.[2–6] Acute maternal HIV infection is associated with increased vertical transmission risk,[7] making prevention of HIV among pregnant and breastfeeding populations a global health priority.[1] WHO and several national HIV programmes recommend offering daily oral tenofovir disoproxil fumarate-based pre-exposure prophylaxis (PrEP) to pregnant and breastfeeding populations at substantial risk for HIV[8–10] on the basis of a large body of safety data from women living with HIV who used tenofovir disoproxil fumarate for HIV treatment during pregnancy and breastfeeding.[8,9,11] Oral tenofovir disoproxil fumarate-based PrEP is scaling up among pregnant and breastfeeding populations in sub-Saharan Africa with notable implementation successes in Kenya and ongoing demonstration projects in South Africa, Lesotho, Malawi, Zambia, and Zimbabwe.[8,12–16] However, adherence to daily oral PrEP is challenging and data suggest that the transitional periods of pregnancy and post partum present unique PrEP adherence barriers.[12,17,18] Thus, there is a need for novel, long-acting tools that prevent HIV acquisition in all populations, including pregnant and breastfeeding populations.[19,20]

Novel PrEP agents in the pipeline are promising and will increase HIV prevention options with anticipated improved adherence and protective coverage, including dapivirine vaginal rings,[21] long-acting injectables,[22] and newer oral antiretrovirals developed for treatment now used as PrEP.[23] However, cisgender women, especially pregnant and breastfeeding populations or those of childbearing potential,[24] remain underrepresented in clinical trials of new HIV PrEP agents and are typically excluded due to concerns over maternal and fetal safety and effects on fertility. In general, WHO technical guidance has supported the provision of oral PrEP for pregnant and breastfeeding women.[10] However, important logistical concerns remain that challenge integration of these populations into existing research structures for initial clinical trials of new PrEP agents. Some of these logistical concerns include more intensive ethical oversight, more complex informed consent requirements and safety monitoring for pregnancy and infant outcomes, and additional review processes from the US Food and Drug Administration and other regulatory bodies —all of which could delay time to market for populations other than pregnant and breastfeeding populations. Delays might also complicate roll-out of beneficial drugs. For instance, communicating early safety concerns of dolutegravir use in pregnancy initially limited access to dolutegravir among pregnant and breastfeeding populations until more

robust data were accrued. This experience highlights the importance of gathering pregnancy-specific data on PrEP agents as early as possible in the drug development process.[25–29] Excluding pregnant and breastfeeding populations from clinical trials, in which conditions are carefully controlled and monitored, results in medication prescriptions in routine care with incomplete evidence on safety and efficacy for use in pregnancy and lactation, thereby increasing the risk of harm.[30]

Prohibiting enrolment of pregnant and breastfeeding populations, and exposure to study product if pregnancy occurs, limits the accumulation of safety data and contributes to prolonged inaccessibility to PrEP products among pregnant and breastfeeding populations. Safety risks for women, fetuses, and infants could be present if pregnant and breastfeeding populations are included in clinical trials of new PrEP agents, but this potential risk needs to be considered in light of the strength of evidence for product-specific and class-specific safety, and the harms of exclusion. Excluding pregnant and breastfeeding populations from PrEP clinical trials inhibits accrual of safety data and subsequently puts these populations at risk for potential adverse outcomes if they use the product without these data.[31–35] Furthermore, inadequate data on the pharmacokinetic and pharmacodynamic profiles associated with PrEP agents during pregnancy could lead to suboptimal or undefined dosing for protective benefit. Concerns about the absence of robust safety and efficacy data could restrict access to first-line prevention agents. The time taken from the establishment of daily oral tenofovir disoproxil fumarate-based PrEP efficacy among cisgender women enrolled in the Partners PrEP Study[36,37] to the development of WHO recommendations for use among pregnant and breastfeeding populations was a decade,[38] despite an abundance of safety data for tenofovir disoproxil fumarate use as antiretroviral therapy (ART) among pregnant and breastfeeding populations living with HIV.[11,39–41] To avoid such delays for PrEP agents in the pipeline, intentional efforts must be made to include pregnant and breastfeeding populations in PrEP clinical trials when appropriate.

In some PrEP clinical trials, cisgender women of reproductive age were eligible to enrol but were required to use hormonal contraception throughout their study participation.[36,42–44] Pregnancy tests were given to participants at study visits. If pregnancy was subsequently detected, investigators discontinued women from the study drug. Once HIV prevention efficacy was established for oral PrEP in the Partners PrEP Study, the following open-label Partners Demonstration Project[45] allowed women who became pregnant the option to self-select PrEP continuation. The HPTN 084 study[46] switches individuals who become pregnant from blinded long-acting PrEP to open-label oral PrEP, as the only agent currently licensed in this population. Investigators excluded women who were pregnant at enrolment in all recent clinical safety trials of PrEP (eg, Microbicide Trials Network [MTN]-003 [daily oral tenofovir disoproxil fumarate plus emtricitabine, daily oral tenofovir disoproxil fumarate, or 1% tenofovir gel],[44] Partners PrEP[36] [daily oral tenofovir disoproxil fumarate plus emtricitabine or tenofovir disoproxil fumarate], FEM-PrEP [daily oral tenofovir disoproxil fumarate plus emtricitabine],[47] CAPRISA 004 [tenofovir gel],[48] HPTN 035 [two vaginal microbicides, BufferGel, and 0·5% PRO 2000/5 Gel],[44] MTN-020 [dapivirine ring],[49] IPM 027 [MK-2048 and vicriviroc rings],[50] and HPTN 084 [long-acting injectable cabotegravir][22]).

We have evaluated inclusion of pregnant and breastfeeding populations in recent and ongoing clinical trials of novel PrEP agents for HIV prevention. We advocate for further inclusion of these populations to ensure that they gain rapid and safe access to these novel PrEP agents in high HIV incidence communities. In line with leading ethics guidelines, we recommend careful consideration of relevant data from preclinical studies in pregnant animals, in non-pregnant women, in retrospective observational studies, and pregnancy registries, and the moral imperative to ensure fair representation of pregnant and breastfeeding populations in the clinical research agenda.[33,51]

Novel PrEP agent clinical trials in cisgender women

Several new PrEP methods are under development and evaluation including some that have already shown efficacy (eg, vaginal rings, long-acting injectables, and daily oral pills), and others that are still under investigation (eg, implants, vaginal patches, and combination products; table). New PrEP agents in the pipeline are promising and are anticipated to increase HIV prevention options for cisgender women. These studies are vitally important and will provide some data from pregnant and breastfeeding populations to inform national drug regulatory authorities, national programmes, and clinicians. Inclusion of pregnant and breastfeeding populations in trials is needed to answer questions about safety relative to non-pregnant cisgender women and to evaluate pharmacokinetics, which could influence dose selection during pregnancy.

Adherence to daily oral PrEP might be more complicated in pregnancy and wane during the post-partum period, similar to women living with HIV taking ART for prevention of vertical HIV transmission.[18] Previous studies have shown that some pregnant and breastfeeding individuals using PrEP struggle with adherence and continuation due to various personal, interpersonal (eg, partner or family support), and health-care access or cost-related barriers.[12,15,17] In addition, HIV risk for pregnant and breastfeeding populations might vary, due to post-partum abstinence and changes in sexual activity over time.[6] Side-effects of daily oral tenofovir disoproxil fumarate-based PrEP, like nausea and vomiting, might be exacerbated during pregnancy; the demands of a newborn infant and breastfeeding could detract from PrEP pill taking.[12,15] A pharmacokinetic study in pregnant women (IMPAACT 2009)[69,70] showed that tenofovir diphosphate concentrations in pregnant women were a third lower than in post-partum women, highlighting the importance of understanding protective thresholds for PrEP exposure and metabolism of PrEP drugs among pregnant women. Findings from IMPAACT 2009 also suggest that adherence to daily oral tenofovir disoproxil fumarate-based PrEP could be especially important for pregnant women. Due to known PrEP adherence barriers and the pharmacokinetics of oral tenofovir disoproxil fumarate plus emtricitabine among pregnant and breastfeeding populations, individuals at high risk in these populations are ideal candidates for novel PrEP agents that could address these concerns.

Vaginal rings

The monthly dapivirine vaginal ring[21] is a silicone vaginal ring containing dapivirine, a non-nucleoside reverse-transcriptase inhibitor, under regulatory review for use as

PrEP and evaluation in pregnant and breastfeeding populations in several ongoing and completed clinical trials (NCT04140266, NCT03965923, NCT02808949, NCT02858037, and NCT01617096).

Two clinical trials in cisgender women, published in 2016, showed that the use of the dapivirine vaginal rings (25 mg) reduced HIV acquisition by 27–31% compared with placebo.[64,71] In Malawi, South Africa, Uganda, and Zimbabwe, researchers found that dapivirine vaginal ring use reduced the rate of new HIV infections by 56% among women using them as instructed, and women older than 21 years were more likely to leave the ring in place than younger women.[64,71] The European Medicines Agency issued a positive opinion on dapivirine vaginal rings for use as PrEP, citing that the benefits outweigh the risks for women who are not using oral PrEP.[72] WHO also includes dapivirine vaginal rings in its PrEP recommendations for cisgender women, including pregnant women judged by their clinician to be at high risk of HIV acquisition,[73] and dapivirine vaginal rings have been registered for use in cisgender women in Zimbabwe. Dapivirine vaginal ring exposure occurred among 169 participants who became pregnant while enrolled in MTN-020/ASPIRE;[57] investigators did not note differences in pregnancy incidence or outcomes (eg, live birth, preterm birth, pregnancy loss, congenital anomalies, and infant growth) between randomisation groups. These findings provided support for additional safety and efficacy studies of dapivirine vaginal rings use throughout pregnancy, including prospective inclusion of women who are pregnant or breastfeeding.

The MTN-042 DELIVER (NCT03965923) and MTN-043 B-PROTECTED (NCT04140266) studies were implemented after confirmation of safety and efficacy in phase 3 trials in cisgender women, and are evaluating maternal and infant safety of dapivirine vaginal rings and daily oral tenofovir disoproxil fumarate-based PrEP in pregnant women and their infants. DELIVER (NCT03965923) completed enrolment of the first cohort of 150 women enrolled at 36–37 weeks gestation in April, 2021. Notably, in June, 2021, the interim review panel for the MTN-042 phase 3b study noted no safety concerns in its review of data from the first cohort of 150 participants. In September, 2021, the panel recommended that the study move forward with enrolment of the next cohort of 150 HIV-uninfected pregnant women, enrolled between 30–35 weeks gestation. The third and final cohort to follow will enrol 250 women at 12–29 weeks gestation (Piper J, National Institute of Allergy and Infectious Diseases, DAIDS, personal communication).

B-PROTECTED (NCT04140266), which enrolled breastfeeding mother–infant pairs, reached full enrolment in July, 2021, with completion of all study follow-up achieved in November, 2021 (Piper J, National Institute of Allergy and Infectious Diseases, DAIDS, personal communication). The B-PROTECTED study follows previous research (MTN-029, NCT02808949) showing extremely low concentrations of dapivirine detected in breastmilk of participants using the dapivirine vaginal rings.[52]

Long-acting injectables

Long-acting cabotegravir[22] is an integrase inhibitor, the same drug class that includes the widely used HIV treatment drug dolutegravir, formulated as an injectable administered

every 2 months for long-lasting PrEP. Dolutegravir use in pregnancy was initially excluded due to early data suggesting an association between dolutegravir use and neural tube defects,[74] an association that attenuated greatly in this cohort over time.[75] WHO now recommends dolutegravir as the preferred antiretroviral drug in first-line ART regimens for all populations,[76] including pregnant women. Data from the HPTN 084 trial[46] showed a protective benefit from injectable long-acting cabotegravir PrEP among cisgender women, with an 89% HIV risk reduction compared with daily oral tenofovir disoproxil fumarate-based PrEP. After regulatory approval, injectable long-acting cabotegravir PrEP in cisgender women could help to overcome the various challenges observed with daily oral PrEP adherence. Toxicology studies and pharmacokinetic evaluations of cabotegravir among pregnant women living with HIV have not identified a birth defect risk;[77] moreover, it is important to weigh such theoretical risks against the likelihood of HIV acquisition and vertical transmission. The HPTN-084 open-label extension will include participants who become pregnant and elect to continue on long-acting cabotegravir.[62]

Lenacapavir is a long-acting HIV-1 capsid inhibitor being tested as an injectable PrEP option administered every 6 months. The objective of the Women's HIV Prevention Study[78] is to evaluate the efficacy of tenofovir disoproxil fumarate and emtricitabine and the two combined for PrEP in adolescent girls and young women at risk of HIV infection. The trial is enrolling participants in several sites in sub-Saharan Africa. Participants who become pregnant after being randomly assigned can remain on the study after a reconsent process in which they will be informed of the benefits and risks of continuing to receive the study drug, possible birth outcomes for the child, and information on lactation.[78]

Newer oral antiretrovirals used as PrEP

Tenofovir alafenamide is the newer tenofovir prodrug that has greater intracellular concentrations of active tenofovir diphosphate with oral dosing with potential for fewer adverse events than tenofovir alafenamide plus emtricitabine.[23] Tenofovir alafenamide in combination with emtricitabine has the potential to be an effective PrEP drug with fewer adverse events in pregnant and breastfeeding populations compared with tenofovir disoproxil fumarate plus emtricitabine. Trials of tenofovir alafenamide with emtricitabine as PrEP for cisgender women in South Africa and Uganda are ongoing; however, US Food and Drug Administration approval for tenofovir alafenamide oral PrEP with emtricitabine only covers at-risk cisgender men and transgender women. Regulators excluded cisgender women because of a lack of trial data in this group; however, the current study protocol of tenofovir alafenamide with emtricitabine (NCT02904369) will allow for active dosing in pregnant and breastfeeding populations following reconsent.[79] Furthermore, clinical trial safety and pharmacokinetic data on tenofovir alafenamide use in pregnant and breastfeeding populations are necessary to advance the use of the drug as PrEP during pregnancy and breastfeeding. When started as HIV treatment in pregnancy in the IMPAACT 2010 trial,[28] the dolutegravir, emtricitabine, and tenofovir alafenamide regimen had the lowest frequency of composite adverse pregnancy outcomes and of neonatal deaths compared with the efavirenz, emtricitabine, and tenofovir disoproxil fumarate regimen. The potential advantages of tenofovir alafenamide, both in side-effects and pregnancy safety profile,

support the generation of evidence for use as PrEP in pregnant and breastfeeding populations.

Monthly oral islatravir, 60 mg/month, is under evaluation in a multisite phase 3 trial of 4500 cisgender, non-pregnant, and non-breastfeeding women, at high risk for HIV infection. Unlike tenofovir disoproxil fumarate or tenofovir alafenamide, islatravir belongs to a new class of antiretrovirals, nucleoside reverse transcriptase translocation inhibitors, and has potent activity against HIV-1, HIV-2, and multidrug-resistant HIV strains, making it attractive across broad geographical settings.[80] The ongoing clinical trial among cisgender women compares oral islatravir taken once a month with tenofovir disoproxil fumarate plus emtricitabine, taken once per day (Impower-022; NCT04644029). This study has an allowance for unblinding and continuation of study product during pregnancy if pregnancy occurs during follow-up. Note that this efficacy trial is currently on clinical hold as per US Food and Drug Administration requirements while an unexpected drug related side-effect resulting in a lymphocyte reduction in some participants dosed with islatravir is being investigated.[81]

Other PrEP approaches

Other novel agents such as vaginal films,[66] inserts, transdermal patches,[67] implants and long-acting formulations,[58,65] and multipurpose technologies[58,65] are under development and investigation among cisgender women. As development progresses, planning evaluations that include pregnant and breastfeeding populations will become increasingly important. Pending ongoing and future safety and pharmacokinetic studies, the multipurpose ring containing 200 mg dapivirine and 320 mg levonorgestrel could be a promising option for breastfeeding populations, given emerging data on the dapivirine vaginal rings and the shown compatibility of levonorgestrel with breastfeeding.

Ethical considerations: toward fair participation of pregnant and breastfeeding populations

Clinical trials that evaluate novel PrEP agents in countries with high HIV incidence should ensure that the study design and inclusion criteria consider inclusion of participants when a favourable risk–benefit ratio is met (eg, pregnant and breastfeeding populations in settings where HIV incidence and fertility rates are high among cisgender women). One of the main ethical issues is how to ensure PrEP use in the short-term and long-term is safe and that decisions to continue use of PrEP in pregnant women are based on a robust risk–benefit calculus. The Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES), funded by the US National Institutes of Health, is a 7-year effort to provide actionable guidance for advancing HIV and co-infection research in pregnant women. A 26-member, international working group developed guidance articulating ethically responsible strategies for conducting HIV research in pregnancy.[82,83,84] In addition, the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT)[31] group developed ethics guidance on how to equitably include the interests of pregnant women and their children in vaccine research. PHASES and PREVENT researchers are collaborating with pregnant and breastfeeding populations to develop ethically responsible strategies

for conducting HIV research in pregnancy and in vaccine trials during epidemics, and appropriately caution against denying pregnant and breastfeeding populations access to similar trials for Ebola, COVID-19, or Zika virus.[31,85]

As study teams fulfil these ethical recommendations for research, data can be ethically generated to inform care of pregnant and breastfeeding populations and ensure their interests are prioritised in both research and clinical settings. WHO and IMPAACT have launched a process for accelerating access to ART for pregnant and breastfeeding populations that includes what is needed at each stage of drug development to allow inclusion in phase 3 trials including safety and pharmacokinetics, which can be referenced for PrEP as well. Strengthened national and international surveillance for women exposed to PrEP agents will help ensure that safety is monitored following clinical trial implementation. A new framework is needed in which the harms of excluding pregnant and breastfeeding populations from HIV prevention trials are considered. Inclusion of pregnant and breastfeeding populations in research will ensure that this population and their children benefit from interventions and treatment critical to their health and wellbeing, and support the need to meet ambitious WHO and UNAIDS targets of ending paediatric HIV.

Leading international ethics guidelines also strongly endorse and support research among pregnant and breastfeeding populations.[14,86–88] The Council for International Organizations of Medical Sciences 2016 guidelines[51] recognises the imperative need to design research for pregnant and breastfeeding populations, UNAIDS asserts that pregnant and breastfeeding populations should be eligible for enrolment as a matter of equity, and the HIV Prevention Trials Network underscores the scientific and ethical priority of including pregnant people in trials.[89] The Council for International Organizations of Medical Sciences does not consider pregnant women to be a vulnerable population, and claims that “research designed to obtain knowledge relevant to the health needs of the pregnant and breastfeeding woman must be promoted”.[51] The HIV Prevention Trials Network recommends that the study product be proven safe in preclinical trials with animals and trials with non-pregnant women, and that research with pregnant people be initiated after consideration of the best available data.[90] The Council for International Organizations of Medical Sciences notes the importance of preclinical data and data in non-pregnant individuals. UNAIDS recommends early discussion (and resolution) about when to do pregnancy-specific pharmacokinetic studies (eg, when the candidate drug has enough promise to move into phase 2b, or phase 3). The Microbicide Trials Network has advocated for a proactive approach to designing a clinical research agenda inclusive of pregnant and breastfeeding populations, as evidenced by a large portfolio of protocols spanning 15 years that includes pregnant and breastfeeding populations in various capacities, with complementary qualitative research and community consultation.[91,92]

The Council for International Organizations of Medical Sciences notes that for research interventions that have the potential to benefit the pregnant woman, the fetus, or both, risks must be minimised and outweighed by the prospect of benefit and the HIV Prevention Trials Network takes a similar view. Researchers could assist ethics committee members to perform a risk–benefit analysis by addressing whether there is sufficient evidence to class administration of the study product as an intervention with potential individual benefit,

because in such instances research risks are not capped at minimal, although they must be mitigated and outweighed by potential individual benefit.

Counselling of participants and full disclosure of possible side-effects and harm to the mother and fetus is essential to address concerns about use of antiretroviral drugs during pregnancy. UNAIDS encourages researchers to inform mothers about the risk of teratogenesis to the fetus, risks to breastfed infants, as well as other risks and the Council for International Organizations of Medical Sciences recommends informing pregnant and breastfeeding populations about risk-mitigation strategies. Communication of risks of an intervention should be contextualised against potential benefits and risk–benefit profiles of alternatives.

Next steps

Pregnant and breastfeeding populations cannot be excluded as innovation advances towards new PrEP agents and tools to reduce HIV incidence. Due to a lack of data from clinical trials, many new PrEP agents are not recommended for use during pregnancy and lactation, placing the burden on clinicians to weigh up the benefits and risks of prescribing drugs for pregnant and breastfeeding populations who are at risk of HIV acquisition.

There is a scientific, public health, and ethical imperative to include pregnant and breastfeeding populations in PrEP clinical trials. We endorse the following next steps in research on new PrEP agents in pregnant and breastfeeding populations. The populations should be intentionally involved in study planning, design, conduct, and results dissemination to enhance the scientific and ethical quality of HIV prevention studies. This engagement should be early, sustained, and inclusive of diverse perspectives. Pharmacokinetic evaluations should consider pregnant and breastfeeding populations in the development stage of new PrEP agents that are intended for use by cisgender women. The inclusion of pregnant and breastfeeding populations in PrEP clinical trials should be considered by weighing up the risk–benefit ratio using the best available data. This inclusion should also allow participants who become pregnant while enrolled to continue receiving the study drug with renewed informed consent.

To date, post-marketing surveillance systems, like the antiretroviral pregnancy registry, are underused as a source of safety data for expanding PrEP access. Strengthening pregnancy registry systems to monitor pregnancy outcomes either pre-approval, such as in the MTN-016 EMBRACE pregnancy registry (NCT01209754), or following PrEP use could increase data accrual and lead to more robust safety evaluations using this available tool. Building a framework for involving pregnant and breastfeeding populations earlier in the PrEP product development pipeline, including in early phase 1–2 studies, and establishment of standards for the amount of safety data required for assurance before including pregnant and breastfeeding populations in clinical trials could aid moving away from compulsory exclusion of pregnant and breastfeeding populations in safety and efficacy trials. In addition, development of a standardised algorithm for evaluating the risk–benefit ratio for new PrEP agents and how to responsibly evaluate safety signals among pregnant and breastfeeding

populations would guide appropriateness and timing of including these populations in future PrEP clinical trials, contextualised to particular candidate products.

By providing robust evidence-based information, the HIV prevention field will take a giant leap forward in providing pregnant and breastfeeding populations, their families, and their health-care providers the evidence needed to make informed health decisions and contribute to preventing HIV among these populations and their infants.

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Table:

Summary of new antiretroviral-based HIV prevention products and studies in women, including pregnant and breastfeeding populations (either ongoing or completed)

	Status of PrEP research in cisgender women	Inclusion of pregnant or breastfeeding women in study
Vaginal rings and gels		
Dapivirine ring	MTN-029/IPM 039 phase 1, open-label study[52] assessed the presence of dapivirine in blood, breast milk, and cervicovaginal fluid when delivered via a vaginal ring used continuously for 14 days	The study enrolled 16 healthy, women without HIV at least 6 weeks post partum, who were lactating but not breastfeeding, at two US sites
Dapivirine ring	MTN-043 (B-PROTECTED; NCT04140266) phase 3b, is evaluating safety in breastfeeding mother-infant pairs using dapivirine vaginal rings or tenofovir disoproxil fumarate plus emtricitabine in Malawi, South Africa, Uganda, and Zimbabwe	200 healthy, breastfeeding women without HIV and their healthy infants between 6–12 weeks old
Dapivirine ring	MTN-042 (DELIVER; NCT03965923) phase 3b, is evaluating maternal and infant safety in dapivirine vaginal rings or oral tenofovir disoproxil fumarate plus emtricitabine in pregnant women and their infants; cohort 1 accrual completed in April, 2021; recruitment of pregnant women in Malawi, South Africa, Uganda, and Zimbabwe is ongoing for another cohort	750 healthy, women without HIV who are 18–40 years old, pregnant with a single fetus
Dapivirine ring	Phase 3b open label extensions: MTN 025/H0PE[53] and DREAM (IPM 032)[54]	22 pregnancies in DREAM (IPM 032); 53 pregnancies in MTN-025/HOPE; no congenital anomalies reported, no new safety signals with respect to available pregnancy outcome data in either study
Dapivirine ring	Phase 3 Ring Trial[55] assessed safety and efficacy in South Africa and Uganda	Pregnant and breastfeeding populations excluded; incident pregnancies reported to be the same in both groups
Dapivirine ring	Phase 3 MTN-020/ASPIRE trial[56] assessed safety and efficacy	No differences noted in pregnancy incidence or outcome in 169 incident pregnancies[57]
Dapivirine ring	Phase 2a clinical trial (REACH; MTN-034)[58] enrolled 247 girls and young women in Kenya, South Africa, Uganda, and Zambia to evaluate safety and adherence to vaginal ring with dapivirine and oral PrEP in a crossover trial where they can choose either product or neither	Data among pregnant and breastfeeding populations are not anticipated from this trial due to pending data in MTN-042 and MTN-043
Vaginal tenofovir 1% gel[59,60]	MTN-008[52,59,61] phase 1 study of daily tenofovir 1% vaginal gel use in term and near-term pregnancy appears to be safe and produces low serum drug concentrations;[59,60] the MTN-008 lactation cohort evaluated pharmacokinetics, pharmacodynamics, safety, and adherence profiles associated with 7 days of 1% tenofovir vaginal gel use[59,60]	Pregnancy cohort randomly assigned (2:1) 98 healthy pregnant women for tenofovir or placebo gel for pharmacokinetic sampling; lactation cohort included 17 HIV-1-seronegative breastfeeding mother-infant pairs
Vaginal tenofovir 1% gel[59,60]	MTN-002 phase 1 study, maternal serum drug concentrations were determined and fetal cord blood, amniotic fluid, placental tissue, and endometrial tissue specimens were collected	16 healthy pregnant women scheduled for caesarean delivery who received a single application of tenofovir gel preoperatively[61]
Implants and injectable long-acting formulations		
Long-acting cabotegravir (integrase inhibitor)	HPTN 084 phase 3 study,[62,63] evaluated safety and efficacy of long-acting injectable cabotegravir in cisgender women (completed in 2021) in Botswana, Kenya, South Africa, Uganda, and Zimbabwe	14 pregnancies to date reported on in the long-acting cabotegravir group;[41,64] open label extension to include pregnant women
Implants and injectable long-acting formulations	Islatravir in a small removable implant could provide PrEP for more than 1 year[58,65]	Data among pregnant and breastfeeding populations are not anticipated from ongoing or planned studies
Lenacapavir	Lenacapavir is a long-acting HIV-1 capsid inhibitor being tested as an injectable PrEP option administered every 6 months; the Women's HIV Prevention Study (NCT04994509) will evaluate	Participants who become pregnant after being randomly assigned can remain on the study after a reconsent process

	Status of PrEP research in cisgender women	Inclusion of pregnant or breastfeeding women in study
	the efficacy of lenacapavir and tenofovir alafenamide plus emtricitabine (which are used together in some groups and separately in other groups) for PrEP in adolescent girls and young women at risk of HIV infection in the USA and South Africa	in which they will be informed of the benefits and risks of continuing to receive the study drug and possible birth outcomes for the child and information on lactation (GS-US-412–5624)
Oral formulations of antiretrovirals for HIV treatment as PrEP		
Tenofovir alafenamide and emtricitabine	Phase 1 study of pharmacokinetic and pharmacodynamics and safety study in cisgender women (NCT02904369)	Pharmacokinetic study in pregnant and post-partum women in South Africa planned for 2022 (NCT04937881)
Oral islatravir (MK-8591) once monthly as PrEP	Phase 3 study of oral islatravir in the USA and sub-Saharan Africa including 4500 cisgender, non-pregnant, and breastfeeding women, at high risk for HIV-1 infection; the study will compare oral islatravir taken once a month with tenofovir disoproxil fumarate plus emtricitabine, taken once per day (NCT04644029)	Data among pregnant and breastfeeding populations are not anticipated from ongoing or planned studies
Raltegravir with or without lamivudine to protect from HIV infection (Raltegravir-PrEP)	Phase 4 open-label study determining ex-vivo protection for genital tissue, randomised pharmacokinetic and pharmacodynamics trial randomised according to gender (NCT03205566)	Data among pregnant and breastfeeding populations are not anticipated from ongoing or planned studies
Other novel approaches in the pipeline		
Vaginal films	FAME-04:[66] phase 1 study showed vaginal films to be safe and well tolerated; 78 non-pregnant women without HIV were included	Data among pregnant and breastfeeding populations are not anticipated from ongoing or planned studies
Patches	Emerging formulation strategies for skin permeation are poised to open transdermal drug delivery allowing the development of new patch technologies to deliver antiretroviral drugs that were previously incapable of transdermal delivery[67]	Data among pregnant and breastfeeding populations are not anticipated from ongoing or planned studies
Vaginal insert[58]	Topical inserts deliver drugs to the portal of viral entry (ie, the genital mucosa), with low systemic exposure, and therefore could be safer and have fewer side-effects than systemic PrEP agents; topical inserts include CONRAD's tenofovir alafenamide fumarate plus elvitegravir insert, and a tenofovir disoproxil fumarate plus emtricitabine insert; Population Council and PATH's griffithsin plus carrageenan fast-dissolve insert; Osel's MucoCept lactobacillus vaginal tablet; prototype extended-release elvitegravir osmotic insert, evaluated pre-clinically by CONRAD[58]	Data among pregnant and breastfeeding populations are not anticipated from ongoing or planned studies
Multipurpose products that might incorporate contraception, HIV, or sexually transmitted infection prevention agents in a single product	Early phase 2 trials of pharmacokinetics, safety, and vaginal bleeding in 90-day use of dapivirine plus levonorgestrel ring[68]	Data among pregnant and breastfeeding populations are not anticipated from ongoing or planned studies

We searched PubMed, ClinicalTrials.gov, and HIV trial network protocols to review ongoing or completed studies on new PrEP agents in cisgender women. We identified 14 ongoing or complete PrEP trials of novel agents in cisgender women, and six phase 1–3 clinical trials and open-label extensions in pregnant and breastfeeding populations. Here we summarise new antiretroviral-based HIV prevention products and studies that are either ongoing or completed in women and pregnant and breastfeeding populations. PrEP=pre-exposure prophylaxis.