Coordinating Implementation Science for Cabotegravir (CAB) for Pre-exposure Prophylaxis (PrEP): Focus on CAB for PrEP Implementation Research and Surveillance during Pregnancy and Breastfeeding

AVAC

AVAC/BioPIC and WHO

Wednesday, 2 November 2022, 8am - 10am EDT | Meeting Summary

Introduction

This meeting was part of an ongoing series, started in September 2021, on coordinating implementation science for injectable CAB for PrEP, focussing specifically on CAB for PrEP implementation research and surveillance during pregnancy and breastfeeding[1].

Meeting Objectives:

1. Share and discuss key considerations and plans for implementation research and surveillance of the safety of CAB for PrEP during pregnancy and breastfeeding
2. Identify remaining knowledge gaps and barriers that need to be addressed to scale and ensure equitable access to CAB for PrEP during pregnancy and breastfeeding

Context

Pregnancy and the post-partum period are times of heightened HIV risk, yet the HIV prevention options for those who are pregnant or breastfeeding are limited. This population is often excluded from biomedical HIV prevention research, while study participants who become pregnant are often stopped from further use of the study drug. In the HIV Prevention Trials Network (HPTN) 084 study that involved cisgender women, there was a requirement for using long-acting reversible contraceptives. However, some study participants became pregnant during the trial and, while CAB was discontinued, the long pharmacokinetic half-life of the drug meant that the effects of residual CAB could be evaluated. Results suggested that residual CAB is generally well tolerated during pregnancy and breastfeeding with no increased risk of congenital anomalies found in those who became pregnant while using CAB for PrEP. However, the number of women exposed remained low and monitoring the use of CAB for PrEP during pregnancy will be necessary as CAB for PrEP programmes are implemented.

Current Guidance on Use of CAB for PrEP during Pregnancy and Breastfeeding

- The WHO guidelines on CAB for PrEP, released in July 2022, state: "While the very limited data available from the small number of women who became pregnant during the studies suggest that CAB for PrEP may be safe during pregnancy and breastfeeding, more research and safety surveillance in pregnancy are needed to monitor adverse pregnancy and infant outcomes, particularly rare adverse events, through the surveillance of PrEP within larger surveillance programmes or Antiretroviral (ARV) pregnancy registries."
- The US Federal Drug Administration (FDA) label for CAB for PrEP states: "Healthcare providers should discuss the benefit-risk of using CAB LA with individuals of childbearing potential or during pregnancy. Cabotegravir use in pregnant women has not been evaluated. Cabotegravir should be used during

[1] While the terms "pregnancy and breastfeeding" were used in this meeting, AVAC and the WHO acknowledge there are a variety of terms being used to refer to these populations, and the discussion around language continues to evolve.

pregnancy only if the expected benefit justifies the potential risk to the foetus." (Section 8.1- Pregnancy) and "Lactation: Assess the benefit-risk of using cabotegravir while breastfeeding due to the potential for adverse reactions and residual concentrations in the systemic circulation for up to 12 months or longer with the injections every two months thereafter after discontinuation."

- Where CAB for PrEP has been registered (Australia, South Africa, USA, and Zimbabwe), the clinical considerations under the product label for use in pregnancy and breastfeeding emphasise the absence of evaluation and the remaining concentration in systemic circulation for up to 12 months or longer after discontinuing injections. The label also emphasises the need for evaluation of risks and benefits.

Monitoring and Surveillance

Ideally, monitoring pregnancy exposure requires knowledge of background rates of adverse pregnancy outcomes in a population not exposed to the agent of interest. There are difficulties in interpreting data without a comparator (e.g., such as a registry approach). Birth outcomes surveillance at sentinel sites may be the optimal approach, and requires an active surveillance program as the drug is introduced. The WHO Global HIV, Hepatitis, and STIs Programmes department has an overall coordinating role in monitoring the safety of antiretroviral use in pregnancy and breastfeeding. The CAB-LA and Surveillance sub-group of the WHO Pregnancy and Therapeutics Working Group (PTWG) is able to support on a harmonised approach for the surveillance of CAB for PrEP during pregnancy and data collection.

Implementation Studies

As of December 2022, there are 23 known planned CAB for PrEP implementation studies. Eleven studies include cisgender women and/or trans men, and three do not target specific populations, meaning there are 14 planned studies that will include people who could become pregnant, implemented across nine countries. Currently, if regulatory approval allows, three of these studies will either recruit participants who are pregnant or breastfeeding (FASTPrEP and PrEP-PP) or allow participants to choose to continue CAB for PrEP if they become pregnant (CATALYST), with study locations in Kenya, Lesotho, South Africa, Uganda, and Zimbabwe. Regulatory applications have been filed in most countries where studies are planned. In countries where the drug has already been approved, the drug market authorisation specifies that use in pregnancy and breastfeeding should be based on a case by case evaluation and provided only if the benefit outweighs the risk for the foetus. As implementation of these studies is being prepared, it is important for national programmes, researchers, funders, policy makers, healthcare providers, and representatives of communities to define a common approach and agree on key considerations on how to include those who are pregnant or breastfeeding, develop key messages for care providers and communities as people choose to stay on CAB for PrEP as they become pregnant, and monitor health and pregnancy outcomes as an integral part of the studies.

Key Takeaways

- Safe and ethical inclusion of pregnant and breastfeeding participants in implementation research will help build robust evidence on use of CAB for PrEP, which will help users, healthcare providers, and regulators make informed decisions.

- ViiV was asked to consider whether its wording on a presented slide- that CAB for PrEP is not recommended by ViiV for use in pregnancy and breastfeeding- accurately captured the safety position for CAB use in pregnancy. The presented wording could be interpreted that ViiV's position is that CAB should not be used during pregnancy or breastfeeding.
  - Post meeting event: ViiV has now updated its complete wording with regard to CAB use in pregnancy and breastfeeding to: "Cabotegravir should be used during pregnancy only if the expected benefit justifies the

potential risk to the foetus AND It is recommended that women breastfeed only if the expected benefit justifies the potential risk to the infant."

- The lack of a specific recommendation during pregnancy/breastfeeding on the CAB for PrEP label is not necessarily a barrier to use by those who are pregnant/breastfeeding. The language on the label is ultimately decided by the local regulator.
- There is an important distinction between a contraindication and the lack of an outright recommendation for a pharmaceutical product. Few drugs unrelated to managing pregnancy-specific conditions are recommended in pregnancy, while many, including common over-the-counter medications, are treated as a risk/benefit discussion between the pregnant/breastfeeding person and their provider.
- Insufficient safety data is currently a significant challenge for implementation projects and national programmes, particularly as initial data from the HPTN 084 Open Label Extension and implementation studies are not expected to be available before 2024.
- In order to provide increased confidence around the use of CAB for PrEP during pregnancy and breastfeeding, regulators would likely want more evidence that the pharmacokinetics are unchanged, a better understanding of any dosage adjustments needed, and evidence regarding key adverse pregnancy outcomes (pre-term birth, low weight birth, stillbirth, and neonatal death) and maternal outcomes.
- Typically, a sample of 200 periconception exposures can rule out a two-fold increase in overall birth defects (prevalence of 3%). It is expected that there are sufficient participants in the HPTN 084 Open Label Extension (OLE) to meet this threshold by the end of 2024. However, monitoring for rare events such as teratogenicity requires large numbers of individuals exposed to product. To rule out a three-fold increase in a relatively rare event like Neural Tube Defect (prevalence of 0.1%), a sample size of 2,000 periconception exposures is needed.
- The adoption of a standardised approach and outcomes will enable implementers to reach a sample size more rapidly by comparing data across sites, regimen, and people exposed vs not exposed.
- The implementation studies evaluating CAB for PrEP use during pregnancy and breastfeeding could build on the approach used for the surveillance of ARVs for treatment during pregnancy to ensure that data collected across PrEP studies were comparable and allow for safety evaluations.
- The MOSAIC team is proposing to host a design meeting to develop a unified pregnancy registry in early 2023.
- With many unknowns about the use of CAB for PrEP during pregnancy and breastfeeding, messaging and early community engagement are critical to ensuring community buy-in. People who are pregnant or breastfeeding do want to minimise the risks of HIV acquisition and transmission to their infant and implementers will need to develop messages around potential risks and benefits to allow people to make informed choices.
- Pregnancy registries are an important tool for longitudinal follow-up and their use is recommended for studies involving pregnant/breastfeeding populations.

CAB for PrEP During Pregnancy and Breastfeeding- Key Knowledge Gaps[2]

Knowledge Gap	Status
Optimal dosing	Will be addressed in HPTN 084 OLE with data likely available by end of 2023
Short-term safety, focused on tolerability and general adverse event profile	Initial insights will be generated by HPTN 084 OLE with opportunities to generate additional evidence in implementation studies
Rare adverse events including foetal loss, preterm birth, foetal growth restriction, and neonatal mortality	Evidence unlikely to be generated at trials so may be generated through post-licensure surveillance- underscoring importance of agreeing a common approach to surveillance across studies, and ultimately systems to allow comparison of those exposed and not exposed to CAB
Data needed by regulators to ensure permissive language on label	The WHO is involved in conversations to answer this question.

Updates from the Think Tank Presentations

HPTN 084 (Sinead Delany-Moretlwe, Wits RHI)
Initial data from HPTN 084 suggest that residual CAB is well tolerated in pregnancy and that pharmacokinetics are comparable to that of those who are not pregnant. Additional questions about optimal dosing and short-term safety will be addressed in the OLE phase.

ViiV Update (Thomas Van Every and Piotr Budnik, ViiV)
At this time, ViiV cannot specifically recommend CAB for PrEP use during pregnancy and breastfeeding and follows the regulatory guidance provided with each approval. ViiV believes CAB for PrEP could have an important role to play in HIV prevention during pregnancy and breastfeeding in Sub-Saharan Africa, provided the safety profile is confirmed. Preclinical toxicology data on CAB for treatment does not indicate a risk to the foetus, and ViiV will gather additional data through its implementation studies in the US: PILLAR, which includes trans men, and EBONI, which includes cisgender women. As CAB is also used in treatment of HIV, further data may be generated from this perspective. ViiV's list of CAB for PrEP submissions and approvals can be found here.

FASTPrEP: PrEPared to Choose Sub-study (Dvora Joseph Davey, UCLA, DTHF, and UCT)
DTHF's FASTPrEP study in South Africa will enrol participants who are pregnant or breastfeeding provided CAB for PrEP is approved for use in pregnancy by the local regulator, SAHPRA. A subset of these participants will be enrolled in the PrEPared to Choose sub study, which will compare PrEP persistence among participants who self-select to use injectable, oral, or vaginal ring PrEP. UCLA in collaboration with UCT is also running a separate study, PrEP-PP, integrating PrEP into antenatal and postnatal care. A PrEP-PP acceptability sub-study found that 74% of pregnant and post-partum women prefer injectable PrEP to oral PrEP.[3]

[2] Adapted from Abrams EJ et al. Journal of the International AIDS Society 2022, 25(S2):e25916.
[3] Wara et al. Preferences and Acceptability for Long-Acting PrEP Agents Among Pregnant and Postpartum Women with Experience Using Daily Oral PrEP in South Africa and Kenya. medRxiv 2022.10.29.22281701. This article is a pre-print.

CATALYST (Lisa Noguchi, Jhpiego)

The MOSAIC consortium's CATALYST study will not exclude participants who are pregnant or breastfeeding, provided that participation is consistent with local regulatory approvals, though the study will not include a clinical sub-study to enrol pregnant or breastfeeding participants specifically. The protocol includes safety monitoring and other procedures to facilitate safe participation for those who are pregnant or breastfeeding. Where possible, CATALYST will link to a pregnancy registry, to follow outcomes beyond the scope of the study.

Perspectives from Ministries of Health (Hasina Subedar, NDOH South Africa; Getrude Ncube, MoHCC Zimbabwe)

- CAB for PrEP is seen as an important intervention to reduce HIV infections acquired during pregnancy and breastfeeding.
- Regulators may require additional safety data on use of CAB for PrEP during pregnancy and breastfeeding before making a recommendation, including data on drug interactions.
- In addition to determining whether to recommend CAB for this population, regulators may need to determine what special precautions and monitoring may be needed.
- In Zimbabwe, where CAB for PrEP was recently approved, the label states that it should only be used during pregnancy if the expected benefit justifies the potential risk to the foetus.
- Gender dynamics will need to be addressed to ensure successful scale-up of CAB for PrEP during pregnancy and breastfeeding, particularly where a male partner does not support use of CAB for PrEP during this time.
- Pregnancy registries are seen as an important monitoring tool.

Recommendations and Way Forward

- As implementation studies are being scaled up, technical partners should carefully consider how to best inform and monitor people who will become pregnant while taking CAB for PrEP, and implement research/surveillance of maternal and pregnancy adverse outcomes. This will support the generation of evidence on the safety of CAB for PrEP during pregnancy and breastfeeding to inform HIV prevention policy in this population.
- Where possible, researchers who include those who are pregnant and breastfeeding in their studies should link to a pregnancy registry to facilitate longitudinal follow-up and inclusion of additional relevant maternal and infant outcomes.
- The CAB-LA and Surveillance sub-groups of the WHO PTWG are working on draft technical guidance to advise technical partners on a harmonised approach and end points for data collection across sites. Birth outcomes surveillance at sentinel sites may be the optimal approach, and requires an active surveillance program as the drug is introduced. WHO will be sending out a survey to better understand current data collection plans on safety during pregnancy and breastfeeding in implementation projects, which will inform future coordination and data synthesis.
- To progress work on a unified registry for CAB for PrEP research in pregnant and breastfeeding populations, the MOSAIC team will keep partners and implementers informed about plans for a design meeting in early 2023, and WHO will link this effort to the CAB-LA and Surveillance sub-groups of the WHO PTWG to harmonise data collection. This work will help ensure pregnancy and birth outcomes across studies are comparable.

- WHO will reach out to implementing partners regarding data collection on safety in pregnancy and breastfeeding to ensure overall coordination and data synthesis.
- Messaging around use of any drug during pregnancy and breastfeeding can be complicated and nuanced; AVAC has committed to working with partners and community representatives to develop specific messaging on these issues to ensure all are aligned.
- AVAC is currently developing the BioPIC Think Tank calendar for 2023; partners should share particular issues they wish to be covered with Catherine Verde Hashim.
- To keep the Implementation Science Tracker up to date, all additions and changes should be shared with Catherine Verde Hashim.

Additional Resources:

Resources relating to pregnancy and breastfeeding:

- More than Vessels: Pregnant people deserve inclusion in HIV prevention clinical and implementation research, December 2022
- The importance of assessing and addressing mental health barriers to PrEP use during pregnancy and postpartum in sub-Saharan Africa: state of the science and research priorities, October 2022
- PrEP for Pregnant and Breastfeeding People Clinical Guidelines Training Package, September 2022 (featuring resources for oral PrEP and the PrEP ring, with resources on CAB for PrEP coming soon)
- Including Pregnant and Lactating Populations in HIV Prevention Research, August 2022
- An Advocate's Guide to Research in Pregnant and Lactating Populations, August 2022
- Surveillance of ARV safety in pregnancy and breastfeeding: towards a new framework, July 2022
- Approaches to accelerating the study of new antiretrovirals in pregnancy, July 2022
- Long acting cabotegravir: updated efficacy and safety results from HPTN 084, July 2022
- WHO Guidelines on Long-Acting Injectable Cabotegravir for HIV Prevention, July 2022 (statement on pregnancy and breastfeeding on p18)
- Phase 3B, randomized, open-label, safety study of dapivirine vaginal ring and oral emtricitabine 200mg/tenofovir disoproxil fumarate 300mg tablet in breastfeeding mother-infant pairs, July 2022
- Evaluation of CAB for PrEP Safety in Pregnancy from HPTN 084, February 2022
- Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners, March 2018

Previous BioPIC Implementation Science Think Tanks:

- Focus on Delivery Models- Report, June 2022
- Coordinating Implementation Science for CAB for PrEP- Report, April 2022
- Implementation Science Questions, April 2022

CAB for PrEP resources:

- Accelerating access and introduction of injectable CAB for PrEP, June 2022
- CAB for PrEP Implementation Study Tracker, October 2022