

**HPTN 084 Open-label Extension Amendment**  
**Community Consultation**  
**Friday, 28 May 2021**  
**Meeting Summary**

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**Executive Summary**

The HIV Prevention Trials Network (HPTN) convened a community consultation for the HPTN 084\* Open-label Extension (OLE) amendment on Friday, 28 May 2021. This meeting, part of an ongoing stakeholder engagement strategy, included approximately 100 attendees from eight countries including civil society leaders, clinical research site investigators and community educators, community advisory boards, and protocol team leadership who participated in the 2016 and 2017 HPTN 084 consultations. The countries conducting HPTN 084 that were represented at this meeting include Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe. The anticipated outcomes of this meeting were discussion and mutual understanding around HPTN 084 OLE, relaxed contraceptive requirements, and actively dosing with cabotegravir (CAB LA) during pregnancy and breastfeeding was achieved.

The consultation presentation included the following topics:

- Pregnant and Breastfeeding Women in Clinical Trials
- Pregnant and Breastfeeding Women in HPTN 084
- Open-label Extension (OLE) Amendment
- Active CAB LA Dosing During Pregnancy

Polling questions about study participants' and partners' reactions to active dosing with CAB LA during pregnancy and breastfeeding were raised throughout the presentation to engage consultation attendees in discourse.

Attached consultations materials are as follows:

- Meeting agenda
- Presentation
- List of invitees

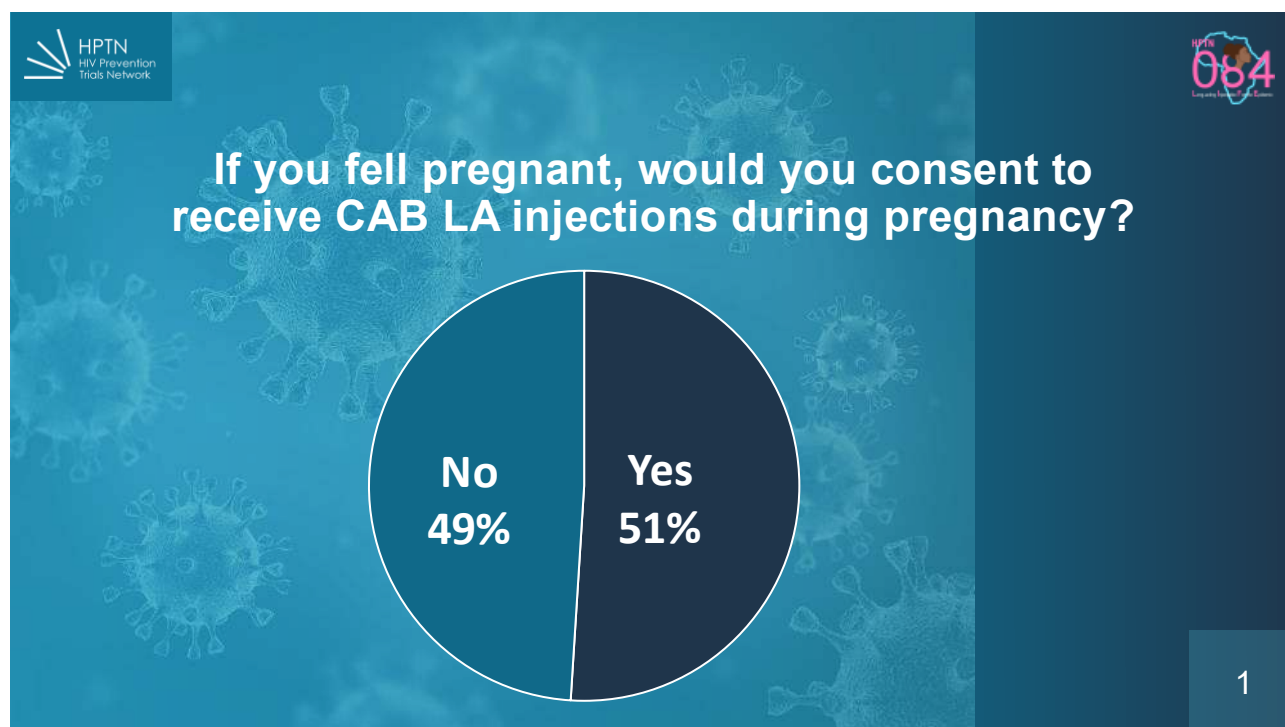
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### Meeting Summary

Consultation co-moderator and HPTN Community Working Group Co-chair, Ntando Yola, welcomed attendees and described the purpose of the two-hour meeting. Attendees were urged to share their comments and questions to support continued preparations for the implementation of HPTN 084 OLE. HPTN Leadership and Operations Center (LOC) Community Engagement Program and Research staff and were acknowledged for organizing and facilitating the meeting. Nandi Luthuli, Regional Stakeholder Engagement Manager with AVAC, introduced the consultation presenters: Dr. Sinead Delany-Moretlwe, HPTN 084 protocol chair, and Dr. Mina Hosseinipour, HPTN 084 co-chair.

Dr. Delany-Moretlwe emphasized the importance and value of the consultation discussions towards enabling the HPTN 084 OLE amendment to accommodate a wide range of perspectives before it is submitted for approval. A polling question was raised at the start of the consultation to assess attendees' thoughts around consenting to receive CAB LA injections during pregnancy. Before commencing a presentation around what is known about the inclusion of pregnant and breastfeeding women in clinical trials and the study leadership team's rationale for the OLE design, a polling question was raised, and the results and responses were discussed.



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## Inclusion of Pregnant/Breastfeeding Women in Clinical Trials

A consultation attendee explained that she responded ‘no’ to the poll because of the information available and her related feelings. She learned that CAB LA and dolutegravir (DTG) worked in a similar way to treat HIV infection and that they were part of the same drug family. Preliminary information about DTG and the Botswana Tsepamo Study indicated that some of the women who fell pregnant while taking DTG had babies with neurological defects of the brain and spine. As a result of findings from Tsepamo, HPTN 084 study participants were advised to use long-acting reversible contraceptives to avoid falling pregnant and experiencing possible birth defects. She questioned how the research team plans to bridge the gap in knowledge from what participants and communities previously learned from the Botswana DTG study and the most current DTG findings. Since DTG information was not conclusive, she questioned whether there is new data on DTG’s safety during pregnancy that might help explain to participants why we believe it is now safe for women to actively dose CAB LA during pregnancy.

Dr. Delany-Moretlwe explained that when planning began for HPTN 084 in 2016 and implementation started in 2017 there were no initial concerns from the preclinical data suggesting that there was going to be any toxicity. Participants were required to use a reliable form of contraception, and pregnancy testing was conducted at each visit. Women with a positive pregnancy test discontinued use of study product so the blinded injections, and the blinded pills were not administered. Women were offered open labeled Truvada® so they could continue to protect themselves against HIV, and it was a requirement that pregnancy was confirmed four weeks later. It was understood that some women might have a positive pregnancy test if they tested regularly for pregnancy, but those pregnancies might not persist. In everyday life, where women are not tested monthly for pregnancy, they might experience conception as a heavier period than usual. It was necessary to observe whether these were pregnancies would persist. Once pregnancies were confirmed participants were unblinded and referred to antenatal care. Assessment of infant outcomes were done at the time of delivery, and again when the infant reached one year.

In May of 2018 data became available from a surveillance and birth outcomes study (Tsepamo) in Botswana on women who were living with HIV and taking antiretrovirals at the time of conception and through pregnancy. The study’s research team observed an early signal that generated concern because they saw what appeared to be a higher rate of neural tube defects (NTDs) equivalent to about one in 100 births. This data led to several alerts and also prompted actions in the HPTN 084 protocol out of an abundance of caution. The team did not have data to explain what was happening with DTG. **CAB LA belongs to the same class of drugs, although it is not DTG and not exactly the same as DTG.** The HPTN 084 study team made adjustments in response to the DTG signal:

- All participants were required to use long-acting reversible contraceptives (LARCs). If they chose not to, they were transitioned to open-label Truvada®.

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- Combined oral contraceptives were no longer permitted.
- Once pregnancy was confirmed, an early ultrasound was performed to assess the presence of fetal anomalies and participants were referred to antenatal care.

The HPTN 084 study team knows much more now than when the early signal was observed. More data has accumulated, more women have been observed within the Botswana surveillance cohort, and there are many more pregnancies that have had outcomes. The original safety signal has diminished over time. Updated data presented April 2020 by the Tsepamo investigators explained that their recent observation was about two neural tube defects per 1000 births. It is important to understand that we will potentially observe NTDs in birth, and it may be unrelated to the drugs involved. It is also important to note that the analysis presented in 2020 found that the difference between the frequency of NTDs among babies born to women taking DTG at the time of conception, and those taking other antiretrovirals was no longer statistically significant. This analysis suggests that there may be NTDs that occur for other reasons, possibly folate deficiency at the time of conception. While these new data were reassuring, other research teams across the world conducted their own studies based on the May 2018 findings. They wanted to learn whether they would experience a similar safety signal and try to explain why the 2018 safety signal was observed. Several databases, including former pharmacovigilance databases which generate reports on pregnancy and pregnancy outcomes, looked for additional data to either support or refute this finding. Analyses were done in small databases in high income countries and the World Health Organization's (WHO) database which accumulates data in a large number of pregnancies globally. These studies did not find evidence for increased NTDs in women using DTG or integrase inhibitors. Some of the preliminary basic science data also could not determine a possible mechanism. One of the conclusions that has emerged is that there may be issues related to folate supplementation in some countries where they do not have food fortification like Botswana. This data was very reassuring for those working on HPTN 084. **The protocol team observed that in the pregnancies that occurred in HPTN 084 despite long-acting reversible contraceptive use, there was no evidence of congenital anomalies in those in which the outcomes after 20 weeks of pregnancy were known. It is important to be reminded that CAB LA is similar but not the same as DTG. It is also known that other studies where pregnant women have taken CAB LA, for example the treatment program, that those research teams have not observed any congenital anomalies in the pregnancy outcomes so collectively the data appears to be reassuring.**

These findings have allowed the HPTN 084 team to embrace conceptual shifts that have occurred across the HIV research community as it relates to thinking about pregnant and breastfeeding women in trials. Those shifts have moved from thinking about women of childbearing potential as a vulnerable population to thinking of them as a complex population. They have unique needs, that should not be a barrier to their inclusion in research. Instead of thinking about protecting them from research there is a need to think about the protections to be gained for large numbers of women by

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including them in research. **Women of childbearing potential should have the opportunity to hear about the risks and benefits of study participation just as like nonpregnant women.**

### **HPTN 084 Open-label Extension (OLE) Amendment**

Dr. Mina Hosseinipour explained that drug absorption, distribution, metabolism, and excretion may change when a woman becomes pregnant and after she delivers. It is possible for pregnant women to experience a lower drug concentration which could present risks of the mother and fetus acquiring HIV. During the postpartum period it is important to have protection from HIV while breastfeeding. In low- and middle-income countries often breastfeeding takes place for a long period of time. We want to avoid withdrawing an effective prophylaxis at a time of increased risk of acquiring HIV. The OLE protocol amendment as described as follows:

#### **Objectives**

- To estimate incidence of HIV among participants who use CAB LA, combining blinded, unblinded and OL periods
- To evaluate safety of open-label CAB LA with and without oral lead-in over 48 weeks
- To evaluate the acceptability (uptake, continuation, discontinuation) of OL CAB over 48 weeks
- To estimate the incidence of pregnancy among participants during the OL period
- To evaluate safety and infant outcomes among pregnant participants
- To evaluate PK of CAB LA among pregnant participants, combined blinded, unblinded, and OL periods
- To describe diagnostic test profile, PK, HIV drug resistance, and response to antiretroviral treatment in those who acquire HIV after CAB LA exposure, combining blinded, unblinded, and OL periods
- To characterize PK and duration of detectable drug among those who discontinue CAB LA injections, combining blinded, unblinded, and OL periods
- To describe levels of Cabotegravir in breastmilk and infants among women who receive CAB LA injections during pregnancy and postpartum

#### **Study Product Options and Visit Schedule**

- Participants will choose either CAB LA or TDF/FTC will be followed for 48 weeks
- Participants switching from TDF/FTC to CAB LA can choose between taking oral CAB for 4 weeks (oral lead-in/OLI) before beginning injections or can immediately start injections
- Most study visits occur every 8 weeks and will be very similar to the blinded study

#### **Amendment Contraceptive Requirements**

- Based on the review of DTG and NTD safety data, participants in the OLE will not be required to use any form of contraception.

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Consultation participants responded to a contraceptive-related polling question:



A consultation participant shared that she responded **no** to the poll. She suggested that perhaps participants might not accept the relaxed contraceptive requirements until it has been fully proven that DTG is safe for use by pregnant women.

### OLE Population

Populations that will participate in the OLE are participants who have ever been enrolled in blinded HPTN 084, and participants in HPTN 084-01\*\*.

### Active CAB LA Dosing During Pregnancy

Dr. Hosseinipour described what is known and unknown about CAB LA during pregnancy:

#### What is known

- Preclinical studies found no effect of CAB LA on embryofetal development.
- There were no congenital defects in babies born to women participating in HPTN 084 or those participating HIV treatment studies.
- Nonpregnant women generally maintained high levels of CAB LA that protected them from acquiring HIV.
- CAB LA was found to be safe and well tolerated in nonpregnant women participating in HPTN 084 and the most common adverse event was injection site reaction.

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- DTG is passed into breast milk at low concentrations of with no side effects experienced by the infant.

### Unknown

- Whether CAB LA is transferred to babies in breastmilk and at what concentration.
- Whether pregnant women metabolize CAB LA differently than nonpregnant women and might require a difference in dosing. Data from the treatment program suggests that no dose adjustments are needed, but more data would be reassuring.
- Whether pregnant women who take CAB LA experience similar rates of side effects to nonpregnant women, or whether pregnancy changes the side effect profile.

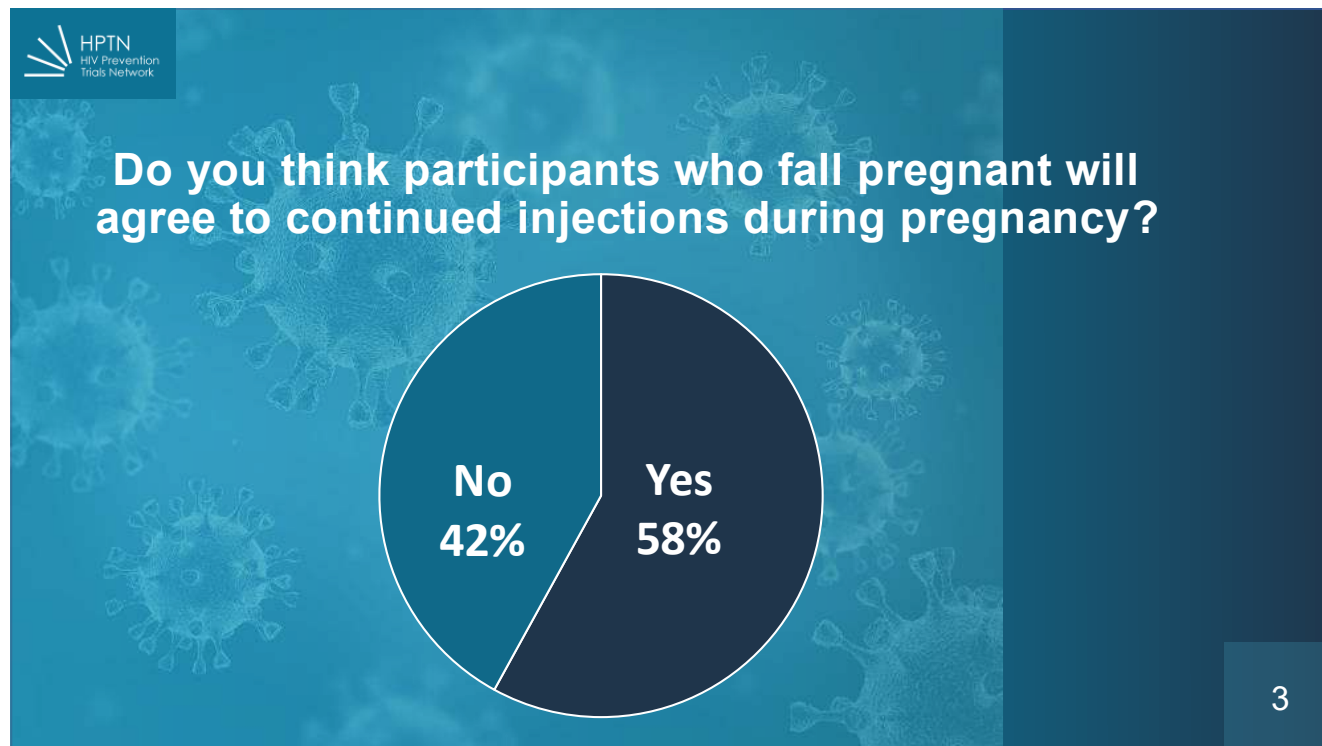
### **Pregnant Women in OLE**

There are increasing numbers of HPTN 084 participants who want to discontinue LARCs and some wish to become pregnant, but they want to continue receiving CAB LA because of it has protected them from acquiring HIV. HPTN 084 study teams want to discuss with women the risks and benefits associated with continued dosing of CAB LA during pregnancy and allow them to decide about whether the risks, which appear to have diminished for DTG, are a greater concern than their concerns about the risk of acquiring HIV. Based on this discussion women would have the opportunity in the OLE to reconsent. If they choose to consent to continuing injections during pregnancy, the study team will monitor them on a monthly basis and assist both mother and the developing fetus through delivery, the postpartum period and to one year of age of the infant. If mothers do not want to continue CAB LA during pregnancy, they will be offered Truvada® for dosing during that period so that they still have the option to protect themselves against HIV. Breastfeeding women will also be given the choice to continue CAB LA while they are breastfeeding. They will be asked to consent to the collection of two additional samples, a collection from the breastfeeding women and from their infants. These collections will allow the study team to understand about CAB LA concentrations in breast milk and in infant plasma in breastfed infants. If they choose not to take CAB LA during that period, they will be offered Truvada® to allow them to have protection from HIV. There are data which indicate that women, during late pregnancy and early postpartum, might be at increased risk for HIV. This is based on some biological changes related to hormonal changes and pregnancy which may increase susceptibility in HIV. For this reason, the study team wants to offer women the benefit of effective HIV prevention during these potentially vulnerable periods.

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Consultation participants responded to a polling question regarding CAB LA injections during pregnancy:



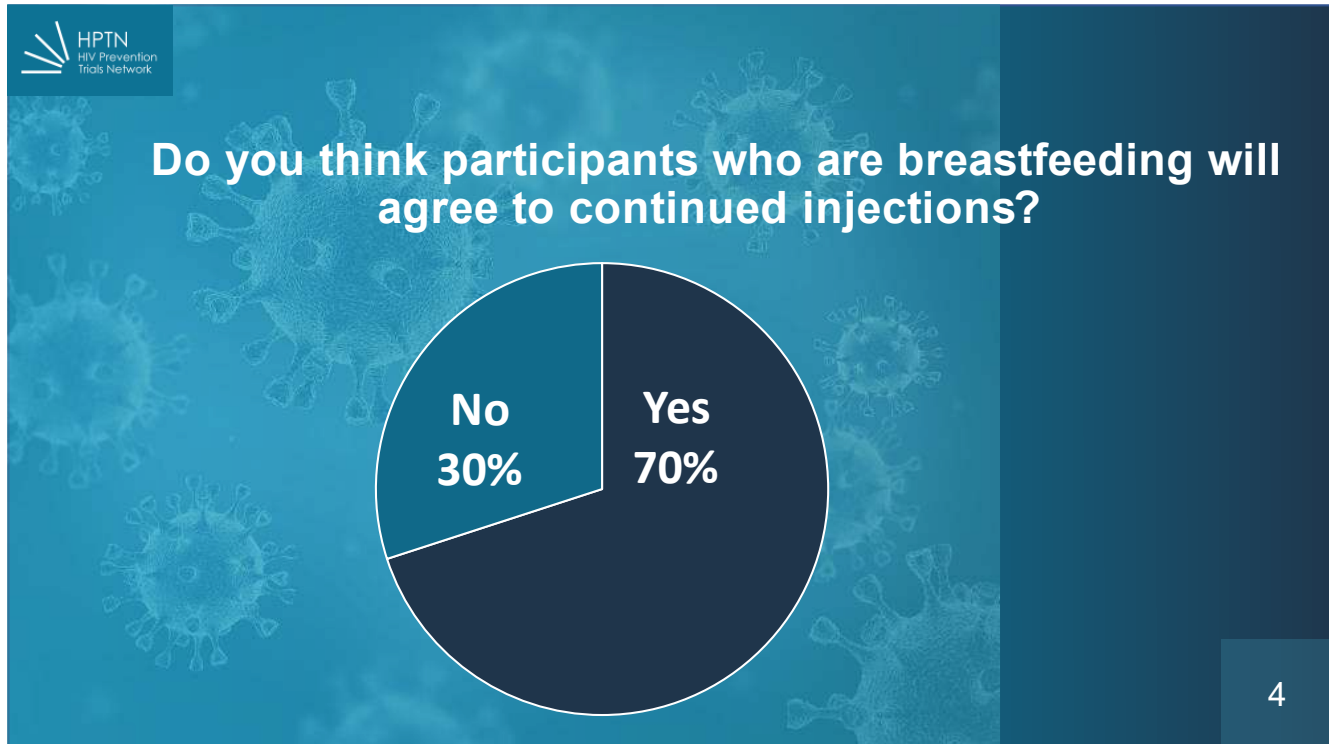
This result suggests that with the provision of information by Drs. Delany-Moretlwe and Hosseinipour, some people changed their mind since the first polling question. Perhaps this indicates that **people need more reassurance which is important for the study teams to know while preparations are underway for the OLE.**

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Consultation participants responded to a polling question regarding the CAB LA injections while breastfeeding:

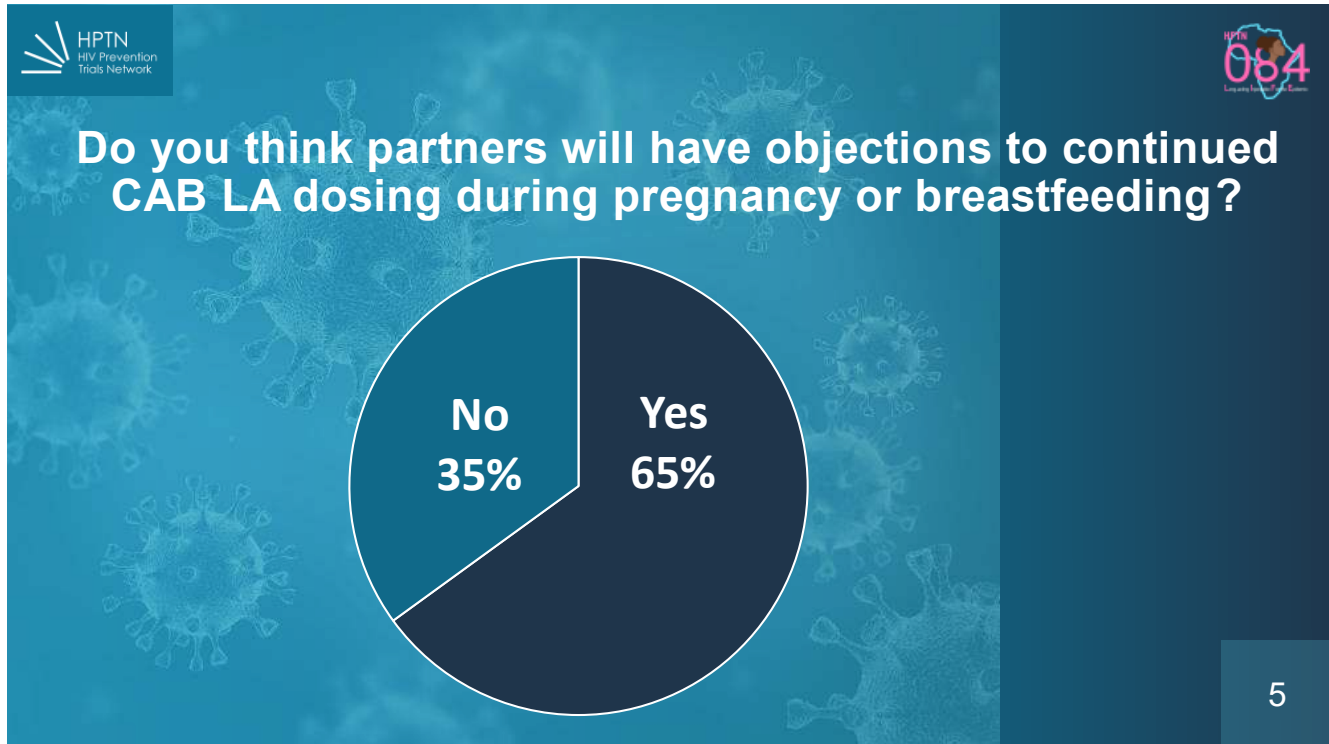


This result compared to the previous one suggests that women might be more cautious about injections during pregnancy but will agree to continue receiving injections during breastfeeding.

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Consultation participants responded to a polling question regarding partner reactions to CAB LA injections during pregnancy and breastfeeding:

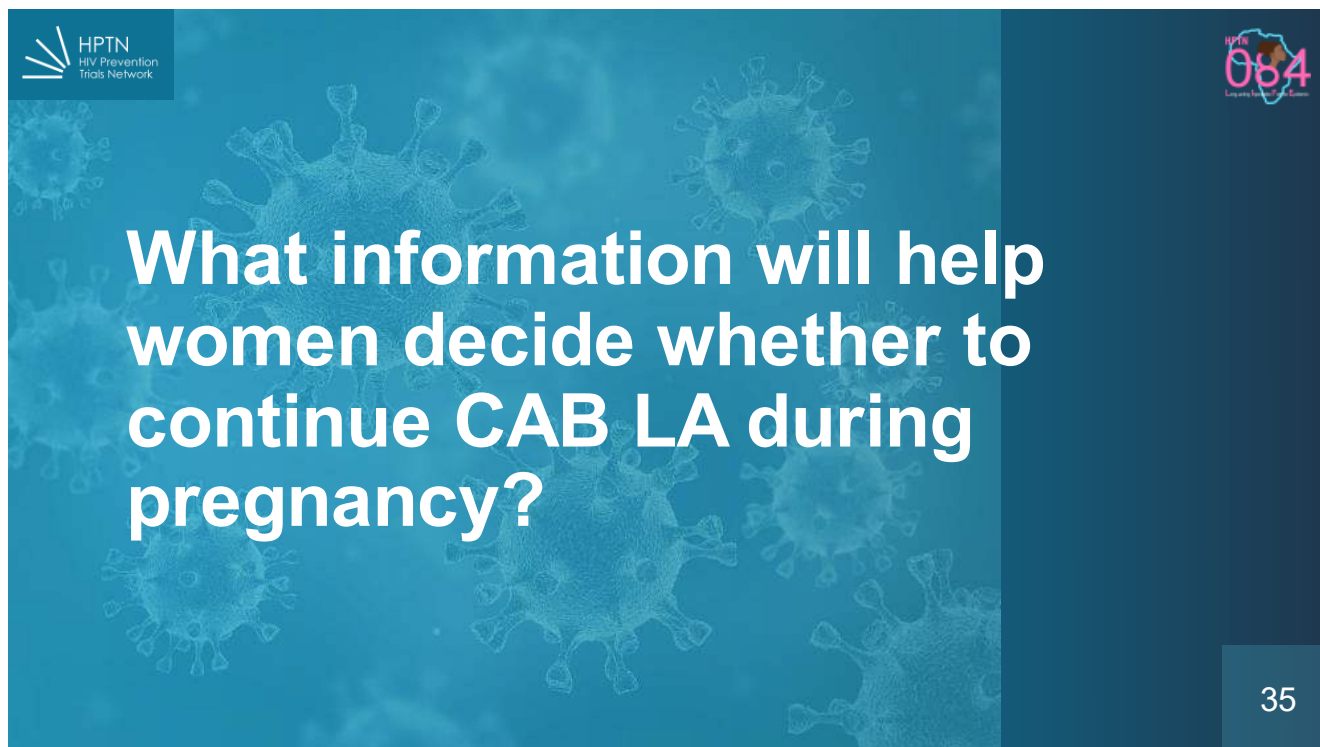


This result highlights that the messaging around the OLE is both for participants and a broader range of stakeholders including partners. People are quite invested in pregnancies and pregnancy outcomes. **This result is really important for the study team.**

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An open-ended question was raised to address anticipated informational needs of women:



Following the presentation, consultation participants raised comments and questions:

*Women are very knowledgeable and want to have as many HIV prevention options as possible. The only information women will need is an assurance that CAB LA will not be harmful to themselves or their unborn babies.*

Nandi Luthuli moderated raising questions and comments in the Zoom chat and responses from Drs. Delany-Moretlwe and Hosseinipour:

Concern was raised about the safety of CAB LA considering that it belongs to the same family as DTG. It was expressed that there is a need for more information on the latest DTG findings and how they relate to pregnancy and some of the birth defects that were previously observed. Development of informational materials, such as a dear participant letter that explains the safety of DTG and how that might relate to CAB LA was recommended.

Dr. Delany-Moretlwe explained that the **reconsent process will consist of a discussion around risks and benefits and an explanation of what is known and what is unknown about CAB LA during pregnancy and breastfeeding**. She noted that women were aware when they joined the blinded trial that there were some unknowns, but **they were interested in the potential of a long-acting injection to protect themselves against HIV which will be important to include in reconsenting discussions**.

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Early in the HPTN 084 study there was a safety signal in DTG which suggested that there may be some harm when used around the time of conception. That concern has diminished with accumulating data. Based on the data available in May 2018, the study team needed to react to the safety signal, but they also knew they needed more data to confirm that. Subsequently that safety signal was something that was seen in the initial data, but **with more time and the accumulation of more data, further events have not been observed. There have been many more pregnancy outcomes and years of follow up, but no additional neural tube defects. WHO has not placed restrictions on women with HIV using DTG.**

There are risks that must be considered, for example the risk that someone might acquire HIV and if that happens during pregnancy then there is also the risk of transmitting HIV to the infant. **In the absence of PrEP, that is a risk of about 4 in every 100 women in one year who might acquire HIV in the countries conducting HPTN 084.** With PrEP as we saw in the study, **using either CAB LA or Truvada<sup>®</sup>, the risk of acquiring HIV could be reduced to about one in every 100 women in one year.** CAB LA is not the same as DTG, and the effect seen in DTG has not been seen in other integrase inhibitors. The safety signal initially observed with DTG has diminished, there is a risk of about two in 1000 pregnancy outcomes.

It is also important to note that **pregnancy itself has risks.** In the absence of drugs or the interventions about three out of 1000 pregnancies may result in an adverse outcome. **A mother will need to decide whether she is worried about the rare event of NTDs that could happen, but is not being shown in CAB LA, or if she is going to worry about the more frequent risk of acquiring HIV and the need to protect herself and her infant.** Women will need support from their communities in making decisions based on risks and benefits and the additional benefits they may derive in the trial such as the opportunity to be closely monitored and linked to care. Also, like in HPTN 084, women's participation could benefit many more women in the future who may benefit from CAB LA once it is licensed.

### ***What is the male involvement plan related to the OLE amendment permitting pregnant and breastfeeding women to actively dose with CAB LA?***

Women who participated in HPTN 084 are the ones who will consent, not male partners. Ultimately, the decision to participate will be made by the participant. Also, there may be reasons why a participant might or might not have disclosed her participation in the trial and her use of PrEP to her partner. The consent will be between the participant and the study sites.

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There were three steps in the study:

1. Oral lead-in
2. Injection Phase
3. Daily oral TDF/FTC for 1 year

The study team observed early on in the study and at many sites that women were discontinuing the study during the oral lead-in because they experienced either pressure from families or partners. Community and stakeholder engagement included discussions about why it might be beneficial for women to be on PrEP. Sites also worked with participants before they joined the trial to help them assess who they would disclose to. Women were encouraged to think about and potentially anticipate what some of the reactions of their families and partners might be. Study teams also talked with them about how and whether it was safe to disclose, whether they would want to, and under what circumstances they would want to disclose. Sites have specific approaches around responding to intimate partner violence, and study leadership will work with sites to ensure that the same approaches adopted in the blinded study will be adopted for the OLE. It is known that women who experienced intimate partner violence are at risk for higher rates of HIV. Perhaps the reason for choosing to participate in the study and accept PrEP is out of concern about the partners' behaviors. Some of these issues are going to be negotiated with regulatory authorities and ethics committees, and there may be site specific decisions. But at a global level, the study team's intention is not to solicit partner consent because ultimately it is the participant who is going to bear the burden of the study. There will be ongoing questions and discussions about who consents. From the study's perspective, researchers are focused on the participant, as she is receiving the study product, she undergoes all the monitoring and study visits, and she is the primary person who should consent. Discussions will happen in households where couples make decisions together about whether or not this is something that they want to do.

One of the aims of the consultation is to learn about the types of questions that may come from partners, participants, and community stakeholders to develop messages about the potential risks and benefits associated with dosing of CAB LA and the reasons why we are taking this cautious but informed approach.

The study team appreciates the feedback raised during the consultation which is that **we have to think about how to support participants to message this to their partners if they do have these discussions**. Communities and stakeholders need to be engaged in presenting the rationale for why women who chose to continue active dosing during pregnancy should be supported in their decision because we believe it is a reasonable decision based on an assessment of the risks and benefits.

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***STI rates in and outside of clinical trials reinforce the need for all PrEP strategies to be delivered in the context of comprehensive, integrated services that include counseling, basic health care, contraception and other sexual and reproductive health services, and linkages to HIV treatment and care.***

In HPTN 084 high rates of chlamydia and gonorrhea were observed. The high rates of syphilis observed in HPTN 083 was not observed in HPTN 084. STIs are a concern, particularly for women who are pregnant because they could have negative consequences for their infant outcomes. As was done throughout the trial and will continue in the OLE, when a participant is diagnosed with STIs they receive treatment and counseling about how to avoid infections in the future. They are also offered opportunities for their partners to be treated. One of the benefits of being in the trial is that women receive laboratory testing every six months which is not the standard of care in many regions where HPTN 084 OLE will be conducted.

Throughout HPTN 084 comprehensive care has been the approach, and most HIV prevention trials do adopt an integrated approach where they are able to provide contraceptive services on site. Because the study included the requirement for LARC, sites also offered an expanded range of contraceptives. In addition to injectables, many women accepted IUCDs, and implants compared to what happens in the public sector. Women in the OLE who fall pregnant will be referred to antenatal services and will receive monitoring during follow-up.

***Will there be a long-term follow-up study to assess whether women and children develop complications in the future after being actively dosed with CAB LA during pregnancy and breastfeeding?***

If women consent to be part of the pregnancy sub study, irrespective of whether or not they decide to continue active dosing with CAB LA during pregnancy, they will be followed up to one year of the infant's life. This aligns with what regulatory authorities require in terms of assessment of initial and late complications. All participants will be followed up to 48 weeks postpartum to assess outcomes in the infant and the mother.

***I think we need to include pregnant women and adolescents in research moving forward. We should take lessons from what we have learned in the context of COVID vaccine studies in terms of messaging and engagement. We raised awareness broadly in the community around the rationale for not giving the vaccines to pregnant healthcare workers, and later when we did vaccinate them.***

It will be helpful to remind people about the approach taken in COVID vaccine research: first to demonstrate that they work, and then to make sure that we are not excluding a population that may be at higher risk for negative outcomes from COVID, and now to include them in trials. This is similar to where we have seen the enormous protective benefits that CAB LA offers. We recognize that for women with new infants that an injectable may be preferred over daily pill taking, but what we want

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is to give pregnant women the option as well. The study team understands the concerns that people may have, but also recognizes that there are enormous benefits that may be derived by being able to offer women a range of effective options for HIV prevention during pregnancy. Now that we know CAB LA works and that it is safe and well tolerated it is important that we work to get as broad a licensure indication as possible so that we do not leave pregnant and breastfeeding women behind.

*For years we have conducted trials where we discouraged women from falling pregnant because of safety issues, so we need to undo that education and information from the last thirty years to move CAB LA among pregnant and breastfeeding women effectively. Other OLE studies conducted a series of consultations with pregnant and breastfeeding women, will the HPTN 084 trial team do something similar?*

Other studies, like The Ring and ASPIRE studies, were completed and then they went on to OLEs, and those studies were completed. Next, they decided to do studies of pregnant and breastfeeding women. What we have learned in HPTN 084 is that taking a step-by-step approach means that it takes a while longer to get data in certain populations like pregnant and breastfeeding women who may be vulnerable to HIV but are left behind, so we are attempting to bring these steps closer together. The Gilead trials of lenacapavir and Descovy, and the Merck Sharp & Dohme Corp trial of Islatravir are going to conduct the pregnancy and breastfeeding trials within their main studies to collect as much data on both pregnant and non-pregnant women at the same time. With CAB LA we want to make sure we can deliver data to the regulatory authorities on safety and drug concentrations in women who become pregnant during the OLE. The extension is part of the original trial. We are amending the current protocol to allow us to move with speed and respond to the recommendations from the DSMB that were issued November 2020 which were to unblind participants and then to ensure that women have access to the effective product. The amendment to the HPTN 084 protocol will allow women to choose. We see this as an opportunity rather than waiting for a new study to collect additional data on safety and pregnancy, and drug concentrations and pregnancy. The aim is that when we submit the data to both the FDA and regulatory bodies within our jurisdictions in which the trial was done, they could go straight to licensing CAB LA as an option for women, irrespective of whether or not they are pregnant. The goal is to shorten these timelines. We are not starting a new study, we are continuing with people who have already used CAB LA or Truvada®. They have been on the study for several years and now we will relax the contraceptive requirements. If they do become pregnant, we will offer them follow-up and an additional intense follow-up. Many of the provisions that existed for HPTN 084 will still exist for the amendment which will last for 48 weeks because we want to know the context of open label use at the end of 48 weeks. At the end of 48 weeks, women have the option of transitioning to an access program that Viiv, who makes CAB LA, will put in place for participants in HPTN 084 until such time as CAB LA is licensed in their country. Participants who want to continue receiving CAB LA can continue to access the product.

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### *What happens to women who have outcomes after 48 weeks?*

With respect to pregnancy, we think that most of the issues that we will see will either emerge early at the time of delivery, or if there are other concerns that come up that are related to developmental issues, we will likely detect those in the first year of life. Regulatory authorities require investigators to assess outcome after deliver and after 12 months. Children grow and develop very rapidly in the first year and acquire many skills. By one year they are walking, saying words and it is very easy to detect developmental delays. After 12 months women will have access to health care in their communities, but we do not expect that if they are experiencing health events that they are related to their participation in the trial.

*The OLE is welcomed as pregnant and breastfeeding women have been concerned about exclusion from research participation. Please say more about the uncertainty around the tail and how messaging around it will be done during HPTN 084 OLE.*

We did not know if someone stopped injections suddenly, because of the long-acting nature of cabotegravir, whether they would have an antiretroviral in their blood for a fairly long period of time. If they were subsequently exposed to HIV, they might acquire an infection which could become resistant to CAB because it is a single drug (monotherapy) which we know resistance develops in this context. Out of an abundance of caution, Step 3 or coverage of the tail was added. Whenever anyone stopped injections, we offered them open label Truvada® so they would reduce their risk of HIV acquisition. At the time that was speculative. What we know now is that across HPTN 083 and 084, we only saw four infections that occurred in people who were receiving cabotegravir. **Out of about 1600 women who received cabotegravir, there were four infections, the HIV incidence was 0.2% in the cabotegravir arm.** Of those four infections, only two of them occurred in women who had actually received injections. Regarding the other two, one who was in Step 1 had never received injections, and she was delayed returning to the clinic. The other person was pregnant and so switched to Truvada and developed infection much later on. In total we have two women who acquired HIV while receiving injections, and there has been laboratory analysis to understand a little bit more about why they might have acquired HIV. We hope to be able to share that in a series of presentations in the coming months. What that data tells us is that none of the women acquired HIV during this tail phase, that is reassuring. HIV infection was really rare, and we did not see any women who acquired HIV infection after stopping injections. There were people who did stop injections, but we did not see any infections in that population. In HPTN 083 they did see some people who acquired infections during the tail phase. They stopped injections and were on Truvada®, they may or may not have been taking it consistently. It was observed that those were not resistant infections which provided the teams with some information that suggests that maybe concern about the tail is not as great of a concern as it was when these trials started. We will learn more about this as cabotegravir is implemented more widely in programs. We also believe that the way we think about this will change

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as we deliver care because we will likely have people coming into clinics to talk about whether or not they want to continue CAB. Part of the conversation should be them assessing their risk for acquiring HIV. If they are no longer at risk for HIV then they do not need to be protected from HIV. But if they are still at risk, they should be using other methods of protection.

***There are populations that are very mobile. They do not come for visits, what do we do about those populations?***

There will need to be a risk-benefit consultation about what are their prevention preferences, what is their ability to engage in programs, what is their HIV risk and based on that, what do they need to protect themselves? Hopefully that conversation yields a set of prevention options that allow people to weigh the risks and benefits and to be aware of this potential concern. They will need to remain engaged in care and if that is something they cannot do, maybe they will choose another HIV prevention option. Maybe they will acknowledge that CAB LA is very effective, and for that reason coming into the clinic every two months for injections is acceptable. Perhaps they will acknowledge their ability to take a pill daily, or maybe they might choose something else like the ring. This will be a conversation between client and a provider.

***I feel strongly that including male partners in behavioral components, such as full group discussion, will enrich study data.***

There have been discussions with the qualitative team about collecting additional data on male partners to understand their reactions. We can have further discussions about what is feasible to do under the amendment.

***Please speak to WHO guidelines.***

There has been a process initiated by WHO and partners in the IMPAACT Network, which is one of the Division of AIDS Networks to explore how we can accelerate access to antiretroviral drugs for pregnant and breastfeeding women. There has been strong commentary about why the HPTN 084 study did not include pregnant and breastfeeding women. We have responded by explaining that we were being cautious about the DTG safety signal. There is a strong desire from normative agencies like WHO but also in country departments of health and regulatory authorities that there is data generated on pregnant women. Data that we will generate in HPTN 084 OLE is about rates of side effects, whether women who were non-pregnant compared to those who were pregnant and received CAB LA have similar drug concentrations which will mean there is no need for dose adjustment. Because we are involving women who were in HPTN 084, we can compare them to their non-pregnant state. We will also collect data about drug concentrations in breast milk, and what that means for the infants in terms of the drug concentrations that they are exposed to.

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There are some questions that the OLE will not answer such as questions about safety of drugs in populations and particularly detecting rare events like NTDs. Those questions will require us to establish pharmacovigilance systems both because of interest in the development in this and other drugs that will be used in pregnant women and the need for us to collect data on pregnancy in much larger numbers. Programs will ultimately answer these questions about rare events. The vaccine field has identified the importance of collecting this information for drugs and vaccines. Pharmacovigilance systems will answer some of the questions that people have about very rare events that might occur, which may be due to chance, or something to do with the pregnancy, or maybe due to use of products which trials can detect.

Reflecting on COVID vaccines and what we have learned, there was not much reporting about blood clots, it was after the trials with large numbers of people using vaccines that there was this concern raised about blood clots. Those events were really rare, small numbers occurring in many millions of people who had been vaccinated. This is where regulatory authorities review the data and make decisions about whether the benefits outweigh the rare outcomes like HIV, SARS-CoV-2, or blood clots.

***Are their concerns about drug interactions with women who switch from Truvada® to CAB LA?***

Triple therapy is used for treatment. CAB has been used in combination with rilpivirine for treatment. We also know that drugs like dolutegravir are used in combination with tenofovir for treatment as well. We do not anticipate there being any drug interactions, we have no concerns about women who want to switch.

***Women have been on study since HPTN 084 and now will move over to the OLE. We are concerned about study fatigue.***

We had an incredible result from HPTN 084, and the study provides women with an opportunity to continue cabotegravir if they so choose. Ideally, we would like them to stay on study during the amendment because we think it will provide them access to a drug that is highly effective in preventing HIV infection. But we understand that some people want to move on with their lives. This is the reason that everyone will re-consent to all the procedures that are associated with follow-up. **We think the greatest incentive is the opportunity to access effective HIV prevention as part of the trial in addition to the benefits that come with being part of the trial, including close monitoring, STI testing, provision of contraceptives, and linkage to HIV care if they seroconvert. In the end, some people may decline, and we will respect their decision.**

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*How will you address cultural issues around pregnancy that cause some women to hide their pregnancy for many months forgoing antenatal care?*

We will continue to offer monthly pregnancy testing, so we will detect women when they are pregnant early on and can work very closely to support those participants. We will work to make sure that as many study sites as possible have arrangement with antenatal and obstetric services because we want to collect samples at the time of delivery and in the early postpartum period. We will work very closely to support participants' access to appropriate antenatal care. They will be followed up monthly and hopefully that will help overcome some of the challenges that happen in real life where people are not tested regularly for pregnancy and do not necessarily have the care that they would receive within the context of a trial.

Drs. Delany-Moretlwe and Hosseinipour thanked consultation participants for their active engagement, Ntando and Nandi for moderating the meeting, and HPTN LOC for organizing and facilitating the meeting. The numerous comments and suggestions will be considered as the study team thinks through the next steps of the amendment. They also committed to continued stakeholder engagement to enable support in messaging the next steps to participants and communities.

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# Meeting Agenda

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## **Including Pregnant Women in Research HPTN 084 Community Consultation Open-label Amendment**

**Call Date: Friday, 28 May 2021**  
**Call Time: 0530 PDT / 0730 CDT / 0830 EDT / 1430 CAT / 1530 EAT**  
**2-hour Duration**

- |   |   |
|---|---|
| <b>1. Welcome and Opening Address</b>                             | <b>Ntando Yola</b>  |
| <b>2. Introduction of Presenters</b>                              | <b>Nandi Luthuli</b>  |
| <b>3. HPTN 084 OLE: Active Dosing Pregnancy and Breastfeeding</b> | <b>Dr. Sinead Delany-Moretlwe<br/>Dr. Mina Hosseinipour</b> |
| <b>4. Polling/Discussion/Questions and Answers</b>                | <b>All</b>  |
| <b>5. Closing Remarks</b>   | <b>Nandi Luthuli</b>  |

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# Consultation Participants

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Aisha Gava	Fiona Nakiyingi	Nandisile Luthuli
Amandah Soza	Friday Saidi	Neetha Morar
Anathi Nqothole	Gift Chareka	Nelecy Chome
Angelo Kaggwa-Katumba	Godfrey Tabata	Neo Nametso Monnapula
Babalwa Matya	Godfrey Ssenyonga	Niru Sista
Barbarah Kawoozo	Jabulile Mantantana	Njabuliso Dlamini
Barbra Nantume	Jennifer Farrior	Nombeko Mpongo
Bekezela Siziba	Jill Stanton	Nombeko Cynthia Mpongo
Bheka Mziyako	Jonathan Lucas	Nombuso Marilyn Zuma
Bongiwe Malinga	Jontraye Davis	Nombuso Ngcobo
Breanne Lesner	Joyce Odenyo	Nomsa Mhlanga
Bridget Jjuuko Ndagano	Juliet Mpendo	Nonkululeko Nzilana
Clifford Gcwensa	Keutloile Praise Moyo	Ntando Yola
Charles Brown	Kevin Bokoch	Ntombozuko Kraai
Charles Chasakara	Khanya Mabuza	Ntsiki Khunju
Cissy Ssuuna	Laura Long	Pepukai Ndadziyira
Clemensia Nakabiito	Likhwa Sithole	Pamela Tshandu
Daisy Ouya	Lilian Birungi	Pamela Grace Mukwekwerere
Daniel Gondwe	Lynda Stranix-Chibanda	Pearson Mmodzi
Definate Nhamo	Marcus Bryan	Philister Adhiambo Madiega
Edith Kibiribiri	Martha Tholanah	Portia Hunidzarira
Elihle Dudula	Mduduzi Dawood Ngubane	Ravindre Panchaia
Elizabeth Magada	Millicent Mbadi	Rebecca Nabukenya
Erica Hamilton	Mina Hosseinipour	Rhonda White
Erick Okioma	Molly Dyer	Samkelisiwe Simelane
Ernest Moseki	Mustafamusa Agwanda	Scott Rose
Eucabeth Awuonda	Patricia Ntege Nahirya	Scovia Aseru

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Sebenzile Mathlaku

Senzokuhle Shibase

Shallon Kabs Kesande

Sinead Delany-Moretlwe

Sibusiso Nhleko

Solethu Nobala

Stanford Chumutimunzeve

Sybil Hosek

Tanette Headen

Tengetile Dlamini

Teopista Nakyanzi

Thoko Makuhunga

Tholakele Shongwe

Tarisai Murefu

Wafaa El-Sadr

Wandile Dube

Xoliswa Nomvungu

Yaw Agyei

Yvonne Atieno Miyawa

Z Mike Chirenje

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# Presentation

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# Welcome

The HPTN 084 Community Consultation will begin shortly

Version 1.0, 28MAY2021

1

## Pregnant and Breastfeeding Women in HPTN 084 Open-label Extension Amendment



**Dr. Sinead Delany-Moretlwe**  
Wits Reproductive Health and HIV Institute and University of the Witwatersrand

**Dr. Mina Hosseinipour**  
University of North Carolina at Chapel Hill and UNC Project-Malawi

28 May 2021




2

### Yes or No

If you fell pregnant, would you consent to receive CAB LA injections during pregnancy?

3



3





## Pregnant and Breastfeeding Women in Clinical Trials

4


### Data from Pregnant and Breastfeeding Women in Clinical Trials

- Pregnant and lactating women are usually excluded from clinical trials to protect the mother and fetus from potential harm which shifts the risk of harm from occurring under clinical trial settings to occurring in routine care settings in which medications may be used despite the absence of data
- The strategy of excluding pregnant and lactating women from clinical trials to avoid harm in fact only serves to increase risk for larger numbers of women who are exposed to medications with uncertain dosing, safety and efficacy data

Hoffman RM et al. Journal of the International AIDS Society 2021, 24:e25580  
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25580/full  
https://doi.org/10.1002/jia2.25580

5

5



Without research, pregnant women...

- may be given drugs at the **wrong dose**.
- may be given drugs that carry **unacceptable risk**.
- may be **denied access** to critically needed drugs.


PHASE Working group, Ending the evidence gap for pregnant women around HIV & co-infections: call to action, 2020

6

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## Data from Pregnant and Breastfeeding Women in Clinical Trials

Addressing use of investigational agents during pregnancy is critically important because populations at risk for HIV are often also at risk for pregnancy



Hoffman RM et al. Journal of the International AIDS Society 2011, 14:e21580  
http://onlinelibrary.wiley.com/doi/10.1002/jia2.21580/full |  
https://doi.org/10.1002/jia2.21580

7

7

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## Pregnancy Data and Drug Approval Timeline

The pace of drug discovery and approval for pregnant and lactating women remains unacceptably slow.

Antiretroviral Licensure → Pregnancy Data  
Approximately 6-year Lag

Hoffman RM et al. Journal of the International AIDS Society 2011, 14:e21580  
http://onlinelibrary.wiley.com/doi/10.1002/jia2.21580/full |  
https://doi.org/10.1002/jia2.21580

8

8

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Statistically Funny.blogspot.com

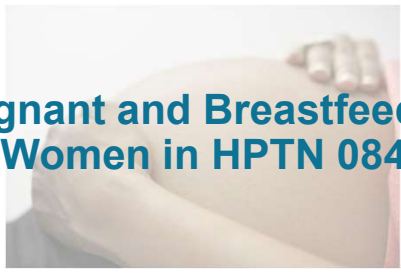
CATCH-22: CLINICAL TRIAL EDITION

04/20/20  
24 May 2011

9

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## Pregnant and Breastfeeding Women in HPTN 084



10

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## Pregnancy and pregnancy prevention during HPTN 084

- No initial reproductive toxicity concerns with CAB LA
- All participants use hormonal contraception
- Pregnancy testing at each visit
- If test positive, hold blinded product
- Offer TDF/FTC
- Confirm test positive 4 weeks later
- If confirmed, unblind and refer to ANC
- Assess pregnancy outcomes at delivery and 12 months

11

11

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## Neural Tube Defects among births from women using dolutegravir at conception:

May 2018, one NTD per 100 births

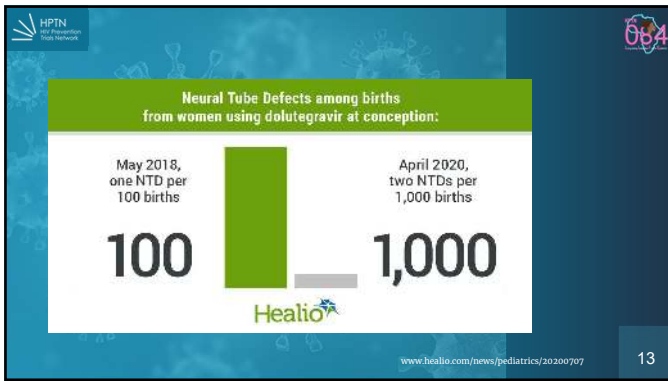
100

Healio

www.healio.com/news/pediatrics/2020/07/

12

12



13

### Pregnancy and pregnancy prevention during HPTN 084

- In response to DTG signal, out of an abundance of caution
- All participants use long-acting reversible contraception (no COC)
- Pregnancy testing at each visit
- If test positive, hold blinded product
- Offer TDF/FTC
- Confirm test positive 4 weeks later
- If confirmed, unblind and refer to ANC
- From May 2018, added early ultrasound for fetal anomalies
- Assess pregnancy outcomes at delivery and 12 months

14

### Neural Tube Defects (NTDs)

New data from the ongoing surveillance in Botswana showed that a further decrease in the difference between prevalence of neural tube defects, or NTDs, among babies born to women taking dolutegravir at conception compared to those that were taking other ARVs. The difference between the groups was no longer statistically significant.

Zash R et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. 29th International AIDS Conference, abstract OAKL0102, 2020

15

### Neural Tube Defects (NTDs)

Other studies using pharmacovigilance databases did not find strong evidence for increased NTDs in those using DTG or other integrase inhibitors

Van de Ven, CID 2020; Chouhara, JAIDS 2019

16

### Pregnancy Outcomes in HPTN 084

	Total n=50	CAB n=29	TDF/FTC n=21
Ongoing	23	15	8
Known pregnancy outcomes n=27			
Live births	20	10	10
Pregnancy loss			
>=37 weeks	0	0	0
20-36 weeks	3	1	2
<20 weeks*	4	3	1
Fetopiric	0	0	0
Congenital anomalies n=27			
No	23	11	12
Unknown	4	3	1

17

### CAB LA and DTG

- CAB is similar, but not the same as DTG and there were no congenital anomalies in HPTN 084 participants who fell pregnant
- We also know that in other research studies where pregnant women took CAB LA, no babies had birth defects

18

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## Conceptual Shifts

Vulnerable population	→	Complex population
Protection from research	→	Protection through research
Presumptive exclusion	→	Fair inclusion

PHASE Working group, Ending the evidence gap for pregnant women around HIV & co-infections: call to action, 2020

19

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## Open-label Extension (OLE) Amendment

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20

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## CAB LA During Pregnancy and Breastfeeding

- Drug metabolism may be different in pregnancy
  - Absorption, distribution, metabolism and excretion may change
  - May be associated with lower exposure and loss of protection
  - Risks of HIV infection to mother and fetus
  - Risk/benefit considerations may be different for prophylaxis
- Post-partum, important to have data on safety during breastfeeding esp. given use in LMIC where prolonged breastfeeding and where risk of HIV infection may be higher in mother

084

21

21

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## OLE Objectives

- To estimate incidence of HIV among participants who use CAB LA, combining blinded, unblinded and OL periods
- To evaluate safety of open-label CAB LA with and without oral lead-in over 48 weeks
- To evaluate the acceptability (uptake, continuation, discontinuation) of OL CAB over 48 weeks
- To estimate the incidence of pregnancy among participants during the OL period
- To evaluate safety and infant outcomes among pregnant participants

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22

22

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## OLE Objectives

- To evaluate PK of CAB LA among pregnant participants, combined blinded, unblinded, and OL periods
- To describe diagnostic test profile, PK, HIV drug resistance, and response to antiretroviral treatment in those who acquire HIV after CAB LA exposure, combining blinded, unblinded, and OL periods
- To characterize PK and duration of detectable drug among those who discontinue CAB LA injections, combining blinded, unblinded, and OL periods
- To describe levels of Cabotegravir in breastmilk and infants among women who receive CAB LA injections during pregnancy

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23

23

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## Protocol amendment

- Participants will choose either CAB LA or TDF/FTC and will be followed for 48 weeks
- Participants switching from TDF/FTC to CAB LA can choose between taking oral CAB for 4 weeks (oral lead-in/OLI) before beginning injections or can immediately start injections
- Most study visits occur every 8 weeks and will be very similar to the blinded study

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24

24

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## OLE Contraceptive Requirements

- After review of DTG/NTD safety data, the long-acting, reversible contraceptive (LARC) requirement will not be required for the OLE
- Participants in the OLE will not be required to use any form of contraception

25

25

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## Yes or No

### Do you think women will accept relaxed contraceptive requirements?


26

26

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## OLE Population

- Participants ever enrolled in HPTN 084 and HPTN 084-01 studies



27

27

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## Active CAB LA Dosing During Pregnancy



28

28

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## CAB LA During Pregnancy

What we know from 084 and previous data	What we would like to learn from the OLE
Pre-clinical studies found no effect of CAB LA on embryofetal development; There were no congenital defects in babies born to women in HPTN 084	
The results of 084 tell us that non-pregnant women generally maintained high levels of CAB that protected them from HIV	Whether pregnant women metabolize CAB LA differently than non-pregnant women and might require a difference in dosing
HPTN 084 showed that CAB was safe and well tolerated in non-pregnant women; the most common AE was injection site reaction	Do pregnant women experience side-effects at the same rate as non-pregnant women?
We know that DTG is passed into breastmilk at low concentrations (3% of plasma) with no adverse events experienced by the infant; we don't know about CAB LA	Is CAB LA transferred to the baby in breastmilk?

29

29

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HIV Prevention Trials Network

## Pregnant Women in OLE

- Increasing numbers of HPTN 084 participants want to discontinue LARCs and some want to become pregnant
- Participants who become pregnant during the OLE will be permitted to continue using CAB LA up to the time of delivery following re consent
  - Adequate monitoring of safety in mother and infant will be provided
- Participants who decline to continue using CAB LA during pregnancy will be offered OLE TDF/FTC

30

30

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**Breastfeeding Women in OLE**

- Participants can remain on CAB LA while breastfeeding
- They will be offered the option to switch to TDF/FTC while breastfeeding if they decline



31

31

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**Yes or No**

**Do you think participants who fall pregnant will agree to continued injections during pregnancy?**

32

32

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**Yes or No**

**Do you think participants who are breastfeeding will agree to continued injections?**

33

33

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**Yes or No**

**Do you think partners will have objections to continued CAB LA dosing during pregnancy or breastfeeding?**

34

34

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**What information will help women decide whether to continue CAB LA during pregnancy?**

35



35



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36

36



# Acknowledgments

- Overall support for the HIV Prevention Trials Network (HPTN) is provided by the National Institute of Allergy and Infectious Diseases (NIAID), Office of the Director (OD), National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH) under Award Numbers UM1AI068619-15 (HPTN Leadership and Operations Center), UM1AI068617-15 (HPTN Statistical and Data Management Center), and UM1AI068613-15 (HPTN Laboratory Center).
- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.



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37