



Refresher training v5 HPTN 084

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Key research questions

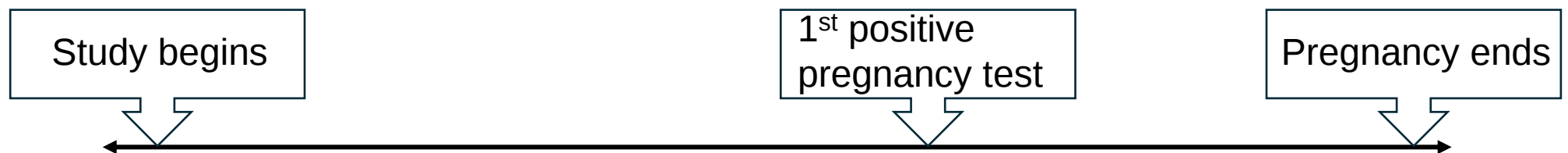
1. **Are the maternal, pregnancy and infant safety outcomes similar between CAB exposed vs. non-exposed, given option for active dosing in OLE?**
2. Do we need dose adjustment during pregnancy (especially in 3rd trimester)?
 - a) Do we need dose adjustment in participants who are steady state on CAB already and then become pregnant?
 - b) Do we need dose adjustment in those that initiate CAB during pregnancy (and therefore not yet at steady state)?
3. What can we say about infant exposure to CAB during lactation?


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graph LR; CAB1[CAB] --> TDF1[TDF/FTC]; CAB1 --> CAB2[CAB]; TDF1 --> Elig1[Eligible sub-study]; CAB2 --> Elig2[Eligible sub-study]; CAB3[CAB] --> Elig3[Eligible sub-study]; TDF2[TDF/FTC] --> CAB4[CAB]; TDF2 --> TDF3[TDF/FTC]; Elig1 --> CAB5[CAB]; Elig1 --> TDF4[TDF/FTC]; Elig2 --> CAB5; Elig2 --> TDF4; Elig3 --> CAB5; Elig3 --> TDF4; CAB5 --> Follow[Follow through to 1 year post-partum]; TDF4 --> Follow; TDF3 --> Comp[Continue follow up and assess outcomes in TDF/FTC group as comparison group];
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The flowchart illustrates the study design progression. It starts with two main groups: CAB and TDF/FTC. The CAB group branches into TDF/FTC and CAB, while the TDF/FTC group branches into CAB and TDF/FTC. Each of these four branches leads to an 'Eligible sub-study'. From the 'Eligible sub-study' stage, participants are either assigned to CAB or TDF/FTC. The CAB and TDF/FTC groups then follow through to 1 year post-partum. The TDF/FTC group that did not consent to follow-up is used as a comparison group for outcomes assessment.

Pregnancy and pregnant participant safety analyses

- Analysis set: all confirmed OLE pregnancies
- Exposure groups:
 - Active CAB: CAB-LA injections during pregnancy
 - Prior CAB: CAB-LA injections prior to, but not during pregnancy
 - No CAB: no CAB-LA injections prior to or during pregnancy



Active CAB	May or may not have CAB-LA	≥1 CAB-LA injections
Prior CAB	≥1 CAB-LA injections	No CAB-LA
No CAB	No CAB-LA	No CAB-LA

Outcomes

Pregnancy outcomes	Maternal outcomes	Neonatal/infant outcomes
Ectopic	Mortality	Neonatal mortality (28 days)
Abortion	Prolongation of hospitalization or re-hospitalization	Infant mortality (first year)
IUFD/Stillbirth	Pregnancy and labor/delivery complications	Hospitalization (first year)
Pre-term birth	Caesarean section (with indication)	Growth (first year)
Small for gestational age (by U/S)	AE associated with pregnancy	Congenital anomalies (48 weeks)
Full-term birth	All grade 2+AE	
Congenital anomalies	Weight gain in pregnancy	

Outcomes selected because they have implications for pregnancy, maternal and infant health

Pre-term birth and low-birth weight associated with negative outcomes

- **Pre-term birth**

- Preterm birth complications = leading cause of death among children under 5 years (35% of deaths among neonates)
- Pre-term neonates who survive has greater risk of short-term and long-term morbidities
- Poor long-term outcomes including cognitive disability, impaired hearing/vision, neurological complications, infections, and chronic pulmonary, cardiovascular, metabolic, and renal disorders (especially in very preterm babies)
- Associated with significant costs to the health system, and families
- Low-birth weight (or small for gestational age) babies are at significantly higher risk of poor health outcomes (including mortality), particularly in low-income settings

V5 updates

Version 2

pregnancy outcomes will be reported on relevant CRFs. Outcomes meeting criteria for expedited AE (EAE) reporting also will be reported. Infants will be followed up for one year post-natally to ascertain final pregnancy outcomes in respect to congenital anomalies.

Version 3, 4 ICF

We know that many women wish to conceive safely, but are worried about the risk of HIV during pregnancy and breastfeeding. If you become pregnant during the study you will be given the chance to continue taking CAB LA injections during pregnancy and breastfeeding. If you prefer, you can switch to TDF/FTC. TDF/FTC has been used much longer than CAB LA and is not known to cause any health problems for babies. All women who become pregnant in the study will be followed up. We would like to know about the health of your baby when born and again at one year of age.

For women who have received at least one CAB LA injection in this study, we would like you to invite you to complete additional study visits during pregnancy and for about one year after the birth of your baby. You will have 11 study visits that are very similar to study visits that occurred before you were

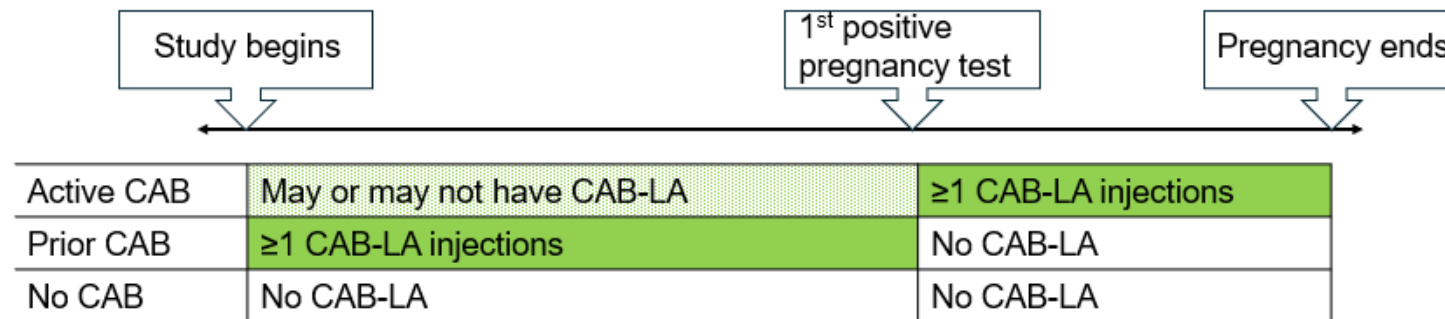
Version 5

Pregnant participants who received at least one CAB injection but who decline participation in the pregnancy and infant sub-study (Step 4d) will not be able to receive CAB LA injections during pregnancy and will be followed according to Step 5. They will not be required to complete pregnancy testing once pregnancy confirmed per the Step 5 SOE. They will be asked to consent to provide updates on any SAEs as well as to consent to live infant assessment of growth parameters at delivery and 48 weeks post-delivery. Site staff will refer pregnant participants for pregnancy care and an ultrasound.

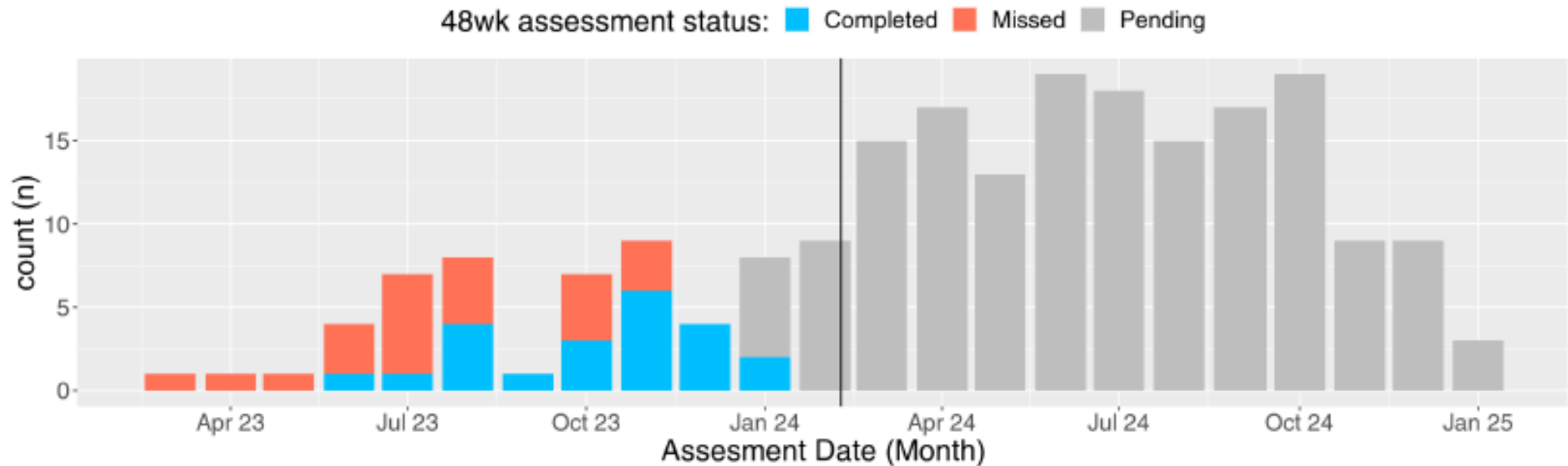
- Since v2, had an interest in birth outcomes through to 48 weeks
- Limitations with initial data collection
 - Update to outcome form
 - Not able to track outcomes of interest effectively
- Now have greater visibility of infant follow up and have observed that we need to strengthen systems for collection of infant outcomes through to 48 weeks – for ALL PREGNANCIES

Importance of a comparator group

- Very important to collect contemporary outcomes data in medication-unexposed comparator group in the same locations/populations
 - Cautious use of “Background” rates from the most comparable population are a far less desirable alternative, if contemporaneous data from comparator group not feasible



Completeness of infant assessment data



Want to focus on collecting complete information in those with missing information

Want to ensure that we are prepared for data collection on future infants

AE reporting in 4d

mother, and blood samples will be collected from the infant (see Step 4d SOE). Infant outcomes will be assessed at delivery and again approximately 11 months later (Week 48 of Step 4d). Assessments of infant feeding and Grade ≥ 2 AEs will be performed at scheduled follow up visits from delivery to Week 24. SAEs, including deaths and congenital anomalies will be reported throughout the 11-month post-partum period (48 weeks).

- SAE will be reported for ALL infants for first 48 weeks of life.
- In addition for 4d only,
 - report grade 2+ AE during first 24 weeks post-partum i.e. during breastfeeding when likely maximum CAB exposure
 - Report irrespective of breastfeeding status
 - Feeding status is captured elsewhere

Next steps

- Refresher training in
 - Ultrasound data collection
 - outcome data collection for infants at 48 weeks