HPTN
HIV Prevention
Trials Network

HPTN 084
Long-acting Injectable For the Epidemic

HPTN 084 Protocol Version 3.0 (OLE) Training

A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

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Monday, 22 November 2021
Training Deck, FINAL, presented 22Nov2021
For Remote Training

Purpose of the OLE

Allow participants who were initially randomized to TDF/FTC to switch to CAB LA

(All participants may choose between either open-label CAB LA or open-label TDF/FTC for 48 weeks)

OR

Protocol v3.0 Objectives

All participants

- To estimate the **incidence of HIV** among participants who use CAB LA, combining blinded, unblinded and OL periods
- To evaluate the **safety** of open-label CAB LA with and without an oral lead-in over 48 weeks
- To evaluate the **acceptability** (uptake, continuation, discontinuation) of OL CAB LA over 48 weeks
- To describe the **diagnostic test profile, PK, HIV drug resistance, and response to antiretroviral treatment** in those who become infected after CAB LA exposure, combining blinded, unblinded and OL periods
- To characterize **pharmacokinetics** and duration of detectable drug among those who discontinue CAB LA injections, combining blinded, unblinded and OL periods.

Pregnant participants

- To estimate the **incidence** of pregnancy among participants during the OL period
- To evaluate **safety and infant outcomes** among pregnant participants
- To evaluate the **PK of CAB LA** among pregnant participants, combining blinded, unblinded and OL periods
- To evaluate **CAB concentration in breastmilk and infants** among women who receive CAB LA injections during pregnancy and/or the early post-partum period.

Overview of New Steps in OLE

1) **Step 4a-** Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first
2) **Step 4b-** Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit
3) **Step 4c-** Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC
4) **Step 4d-** Procedures for Pregnant/Breastfeeding Participants
5) **Step 5-** Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation
6) SOE for Participants who Acquire HIV on v3.0

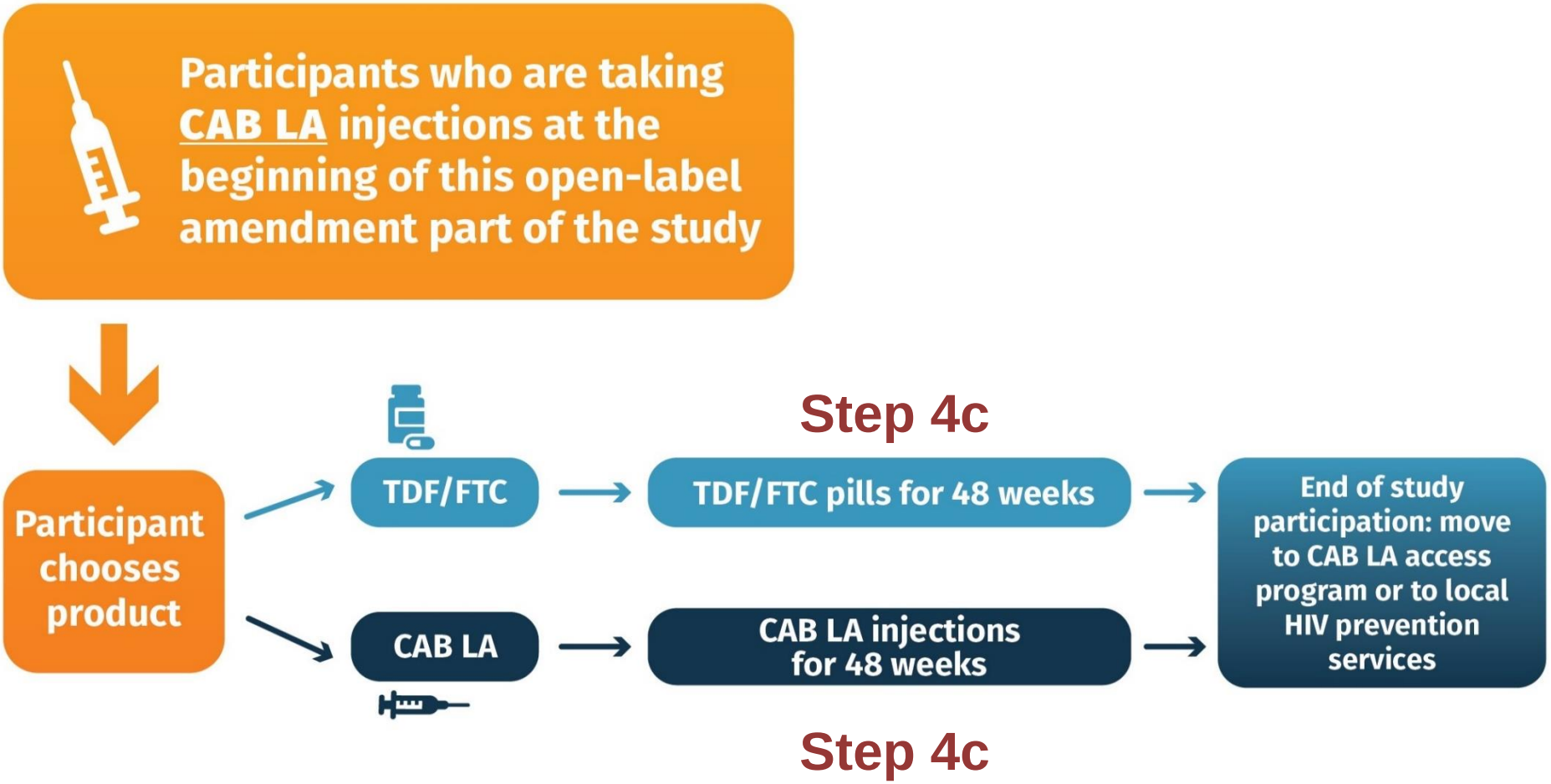
Step 4c: Maintenance Dosing

- **Step 4c-** Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC

OR

Clinic visits every 8 weeks, for 48 weeks

Step 4c: Options for Participants on CAB LA at Implementation of v30



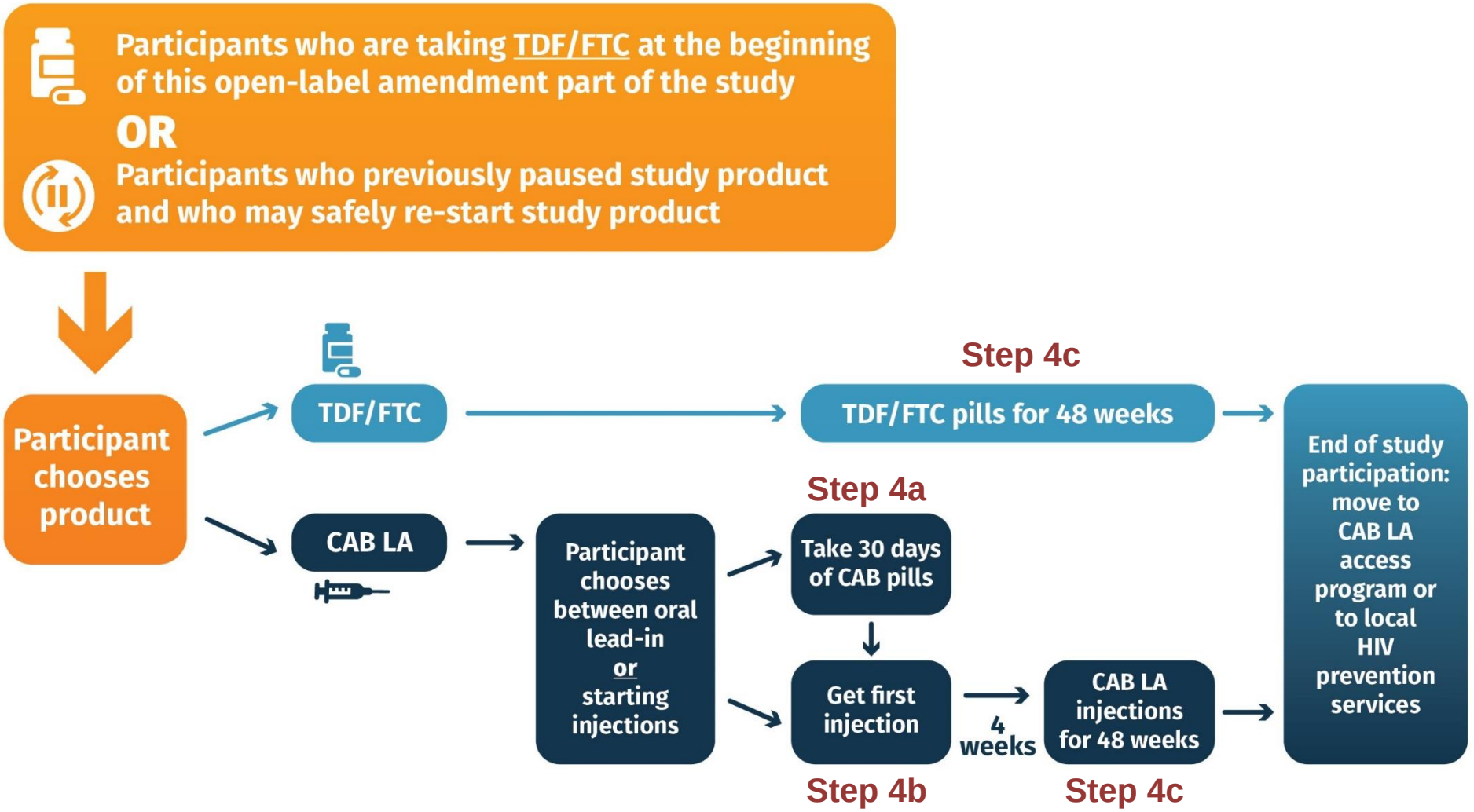
Steps 4a, 4b and 4c in v3.0

- **Step 4a-** Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first

- **Step 4b-** Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit

- **Step 4c-** Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC

Steps 4a, 4b and 4c: Options for Participants on TDF/FTC at Transition



4a: SoE for those on TDF/FTC who want CAB with Oral Lead-in

	DAY 0/ of Step 4a
ADMINISTRATIVE, BEHAVIORAL, REGULATORY	
Informed consent	X
Locator information	X
Offer CAB LA and counseling on direct to inject vs. oral lead in	X
Acceptability assessment	X
Behavioral assessment	X
HIV prevention counseling	X
Offer condoms	X
CLINICAL EVALUATIONS & PROCEDURES	
Medical history, con meds, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X
Blood collection	X
Urine collection[1]	X
For those who select oral lead in: Dispense study product (enough for 4 weeks)	X
Adherence counseling[2]	X
LOCAL LABORATORY EVALUATIONS & PROCEDURES	
HIV testing[3]	X
HIV viral load testing[4]	X
Pregnancy testing[1]	X
CBC with differential, if not done in Step 4a	X
Chemistry testing[5]	X
Liver function tests[6]	X
Fasting lipid profile, if not done in Step 4a[7]	X
Plasma storage[8,9]	X
DBS storage[9]	X

4b: SoE Initiating or Re-starting CAB LA w/o Oral Lead-in (Initial Dose Visit)

	DAY 0 of Step 4b
ADMINISTRATIVE, BEHAVIORAL, REGULATORY	
Informed consent, if not obtained in Step 4a	X
Locator information	X
Offer CAB LA and counseling on direct to inject vs. oral lead in, if not done in Step 4a	X
Acceptability assessment, if not done in Step 4a	X
Behavioral assessment, if not done in Step 4a	X
HIV prevention counseling	X
Offer condoms	X
CLINICAL EVALUATIONS & PROCEDURES	
Medical history, con meds, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X
Blood collection	X
Urine collection[1]	X
Adherence counseling[2]	X
Dispense and administer CAB LA ±	X
LOCAL LABORATORY EVALUATIONS & PROCEDURES	
HIV testing[3]	X
HIV viral load testing [4]	X
Pregnancy testing[1]	X
CBC with differential, if not done in Step 4a	X
Chemistry testing[5]	X
Liver function tests[6]	X
Fasting lipid profile, if not done in Step 4a[7]	X
Plasma storage[8,9]	X
DBS storage[9]	X

4c: SoE Maintenance Doses of CAB LA or TDF/FTC 48 weeks

Time on OL Study Product	Week 0 of Step 4c±		Week 8		Week 16		Week 24		Week 32		Week 40		Week 48
Informed Consent**	X												
Locator information	X		X		X		X		X		X		X
Acceptability assessment	X						X						X
Behavioral assessment	X		X		X		X		X		X		X
HIV prevention counseling	X		X		X		X		X		X		X
Offer condoms per local SOC	X		X		X		X		X		X		X
CLINICAL EVALUATIONS & PROCEDURES													
Medical history, concomitant medications, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X		X		X		X		X		X		X
Blood collection	X		X		X		X		X		X		X
Urine collection[1]	X		X		X		X		X		X		X
Vaginal swab collection[2]	X						X						X
Adherence counseling[3]	X		X		X		X		X		X		X
Dispense/administer product as is appropriate	X		X		X		X		X		X		X

4c: SoE Maintenance Doses of CAB LA or TDF/FTC 48 weeks (Cont.)

Time on OL Study Product	Week 0 of Step 4c±		Week 8		Week 16		Week 24		Week 32		Week 40		Week 48
LOCAL LABORATORY EVALUATIONS & PROCEDURES													
HIV testing[4]	X		X		X		X		X		X		X
HIV viral load testing[5]	X		X		X		X		X		X		X
Pregnancy testing[1]	X		X		X		X		X		X		X
CBC with differential, if not done in Step 4a or 4b	X						X						X
Chemistry testing, if not done in Step 4a or 4b[6]	X						X						X
Liver function testing[7]	X						X						X
Fasting lipid profile[8]													X
Syphilis testing	X						X						X
Vaginal GC/CT and TV testing[2]	X						X						X
Urinalysis (protein, glucose)	X						X						X
Plasma storage[9,10]	X		X		X		X		X		X		X
DBS storage[10]	X		X		X		X		X		X		X

Laboratory Notes

***NEW ***

- HIV RNA testing in addition to HIV rapid and instrumented testing
- Check lab reports and report any detectable VL results regardless of rapid and instrumented results to the HIV alias
- Ensure that data entry on the eCRF is correct - watch the reporting of Detectable versus Target Not Detected

Laboratory Notes, Continued

- Check the footnotes carefully regarding the chemistry analytes.
- Albumin has been added
- CPK, Phosphorous, Glucose, Amylase, Lipase and Calcium have been removed

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6) SOE for Participants who Acquire HIV on v3.0

Managing Pregnant Participants on v3.0

- Confirm the pregnancy: At the first positive pregnancy test visit, confirm the pregnancy on a second independent sample

- Discuss Study Product Options: Allow participants to choose between either open-label CAB LA or open-label TDF/FTC for Pregnancy and Breastfeeding

OR

Note: the last dose of CAB LA to be administered through the study is at 24 weeks post delivery.

Pregnant Participant Chooses TDF/FTC

If a participant has never received CAB LA and does not wish to take CAB LA during her pregnancy. She will be followed on **Step 4c**.

Pregnant Participant Chooses CAB LA

- If a participant wishes to receive CAB LA during pregnancy, she must be counseled about the risks and benefits of receiving CAB LA and she must agree to participate in the Pregnancy and Infant Sub-Study (**Step 4d**); this is a safety measure.

- **Step 4d:** clinic visits every 4 weeks during pregnancy and then shifts to every 8 week at 8 weeks after delivery

Step 4d: Eligibility

- **Step 4d** is an option for participants who:
  1) become pregnant in Step 4 or during the first 8 weeks of Step 5, AND
  2) who have had at least one CAB LA injection ever; regardless of product choice during pregnancy

- Participants who have never taken CAB LA are not eligible for the Pregnancy and Infant Sub-Study

NOTE: Forthcoming CM to clarify that PPTs pregnant at the transition to v3.0 AND who have had previous CAB LA exposure to join the Pregnancy and Infant Sub-Study

4d- SoE Procedures for Pregnant/ Breastfeeding Participants

Time on Pregnancy and Infant Sub-study	Week 0	Wee k 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Delivery	Week 2, pp	Week 4, pp	Week 8, pp	Week 16 pp	Week 24, pp	Week 32, pp	Week 40, pp	Week 48, pp
Maternal assessments																				
Informed Consent	X																			
Locator information	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
Acceptability assessment	X			X					X								X			X
Behavioral assessment	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
HIV prevention counseling	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
Offer condoms per local SOC	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
Medical history, concomitant medications (including folate intake)	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
Targeted physical exam including antenatal assessment per SOC	X	X	X	X	X	X	X	X	X	X	X				X					X
Ultrasound or refer to ultrasound				X																
Blood collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection [1]	X						X								X	X	X	X	X	X
Vaginal swab collection[1]	X						X								X					X
Breastmilk Collection, 5mLs[4]													X	X	X	X	X			
Adherence counseling[2]	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X
Contraceptive counseling															X	X	X	X	X	X
Dispense/administer study product, as is appropriate	X		X		X		X		X		X				X	X	X	X		X
ISR Assessment, only for PPTs receiving CAB LA injections		X		X		X		X		X					X					X

4d- SoE Procedures for Pregnant/ Breastfeeding Participants (Cont.)

Time on Pregnancy and Infant Sub-study	Week 0	Wee k 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Delivery	Week 2, pp	Week 4, pp	Week 8, pp	Week 16 pp	Week 24, pp	Week 32, pp	Week 40, pp	Week 48, pp
Maternal assessments																				
HIV testing[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV viral load testing [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing[5]															X	X	X	X	X	X
CBC with differential	X						X			X					X					X
Chemistry testing[6]	X						X			X					X					X
Liver function testing[7]	X						X			X					X					X
Syphilis testing	X						X								X					X
Vaginal GC/CT and TV testing[1]	X						X								X					X
Urinalysis (protein, glucose)	X						X			X					X					X
Plasma storage[8,9]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Breastmilk storage[9,10]													X	X	X	X	X			
DBS storage for women on TDF/FTC only[9,11]	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X			

4d- SoE Procedures for Pregnant/ Breastfeeding Participants (Cont.)

Time on Pregnancy and Infant Sub-study	Week 0	Wee k 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Delivery	Week 2, pp	Week 4, pp	Week 8, pp	Week 16 pp	Week 24, pp	Week 32, pp	Week 40, pp	Week 48, pp
Infant assessments																				
Pregnancy outcome assessment including abbreviated infant examination[12]															X					X
Infant feeding history															X	X	X			
Infant HIV testing, if the mother is confirmed to have HIV infection[13]																				
Cord blood storage[9,14]												X								
Infant plasma storage[9,14]												X	X	X	X	X	X			X

Laboratory Notes for Step 4d

- Note new collection/specimens
  - Breast milk (sent to the lab on wet ice, processed within 6 hrs.
  - Cord Blood (5ml)
  - Infant plasma

*Infant testing per local guidelines

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6) SOE for Participants who Acquire HIV on v3.0

Step 5: TDF/FTC

- Participants who take CAB LA during the v3.0 protocol and elect to stop taking CAB LA before the 48-week period will be transitioned to **Step 5**

- During **Step 5**, the participants will be given open-label TDF/FTC for 48 weeks

- At the end of **Step 5**, participants will be referred to local HIV prevention services

Step 5- SoE TDF/FTC Tail Coverage ONLY for those who had to Prematurely d/c CAB during the Step 4

Time in Step 5	Step 5, Day 0*	Step 5, Week 12	Step 5, Week 24	Step 5, Week 36	Step 5, Week 48
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
Acceptability assessment	X				X
Behavioral assessment (if done in last 4 weeks, skip D0 and start at W12)	X		X		X
HIV prevention counseling	X	X	X	X	X
Offer condoms	X	X	X	X	X
CLINICAL EVALUATIONS & PROCEDURES					
Medical history, concomitant medications, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X	X	X	X	X
Blood collection	X	X	X	X	X
Urine collection	X[7]	X	X	X	X
Vaginal swab collection[1]	X[7]		X		X
Adherence counseling[2]	X	X	X	X	
Dispense pills to all participants	X	X	X	X	
Plasma storage[8,9]	X	X	X	X	X
DBS storage[9]	X	X	X	X	X

Step 5- SoE TDF/FTC Tail Coverage ONLY for those who had to Prematurely d/c CAB during the Step 4 (Cont.)

Time in Step 5	Step 5, Day 0*	Step 5, Week 12	Step 5, Week 24	Step 5, Week 36	Step 5, Week 48
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing [3]	X	X	X	X	X
HIV viral load testing[4]	X	X	X	X	X
Pregnancy testing[5]	X	X	X	X	X
Chemistry testing[6]	X		X		X
Liver function testing[7]	X				X
Syphilis testing	X7		X		X
GC/CT and TV testing[1]	X7		X		X
Plasma storage[8,9]	X	X	X	X	X
DBS storage[9]	X	X	X	X	X

Overview of New Steps in OLE

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6) SOE for Participants who Acquire HIV on v3.0

Participants who Seroconvert during v3.0

Contact HIV alias

084HIV@hptn.org

Once HIV infection is confirmed, refer to an HIV Care Clinic

Maintain contact with participants until viral suppression is reported

Participants who acquire HIV infection	
	HIV Confirmation Visit
ADMININISTRATIVE, BEHAVIORAL, REGULATORY	
Locator information	X
Offer condoms	X
HIV counseling	X
CLINICAL EVALUATIONS AND PROCEDURES	
History, con meds, physical exam (with pulse, BP, weight and BMI calculated at each visit)	X
Blood collection	X
LOCAL LABORATORY EVALUATIONS	
HIV testing[1]	X
CD4 cell count	X
HIV viral load testing[2]	X
HIV resistance testing[3]	X
Chemistry testing[4]	X
Liver function testing[5]	X
Plasma storage[6,7]	X
DBS Storage[7]	X

Transitioning to v3.0

HPTN 084 Cheat Sheet for Transitioning PPTs from V2.0 to V3.0

Participant Status under v2.0 Protocol	Participant Options under v3.0	Where to Transition the Participant Under v3.0
PPT on TDF/FTC with no contraindications chooses between:	joining v3.0, staying on TDF/FTC	Start with Step 4c
	joining v3.0, transitioning to CAB LA	Offer oral lead in (Step 4a) and straight to injection (Step 4b); Participant chooses; After completing Step 4b move to Step 4c
	joining v3.0, does not want to take either product	Start with Step 4c, but without study product administration
	not joining v3.0	Complete termination procedures
PPT on CAB LA with no contraindications chooses between:	joining v3.0, staying on CAB LA	Start with Step 4c
	joining v3.0, transitioning to TDF/FTC	Start with Step 4c
	joining v3.0 but does not want to take either product	Start with Step 4c, but without study product administration
	not joining v3.0	Complete termination procedures
PPT who is confirmed HIV+ on v2.0 chooses between:	joining 3.0	Consent to v3.0. Contact the HIV alias **AND the CMC**. Follow their guidance for PPT management.
	not joining v3.0	Complete termination procedures
PPT on the Contraceptive Sub-study chooses between:	joining v3.0 and continuing on contraceptive sub-study	Have PPT sign the ICF signature block for continuing the sub-study, Contact the CMC for PPT management
	joining v3.0 and stopping the contraceptive sub-study	Have PPT sign the ICF signature block for declining the sub-study

For participants with less straightforward circumstances, refer to the Cheat Sheet and/or contact the CMC (084CMC@hptn.org)

Transitioning More Complicated Scenarios

HIV seroconversion during v2.0 and within the 48 week schedule (contact HIV alias)

PPT on v2.0 on open-label TDF/FTC because of safety concerns

Contact CMC alias for PPT management instruction

PPT on v2.0 Contraceptive Sub-Study

084CMC@hptn.org

LoA 1 Major Updates

- Added consent forms for partners and providers for those doing the Qualitative Substudy ONLY
- Clarified that fetal ultrasound is to take place at any time within the first 12 weeks
- Study medications should be dispensed at Week 40 in post-partum pregnancy substudy (was left out-TDF/FTC)
- Any participant dosing CAB LA during pregnancy will stop by week 24 post delivery and switch to either CAB access programme or TDF/FTC via study or locally

Important Differences Between v2 and 3

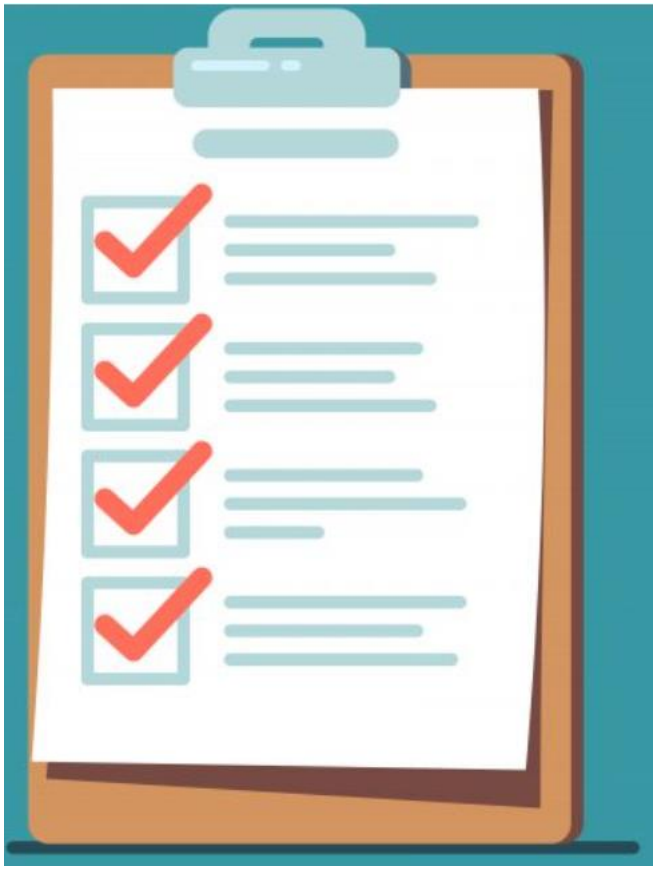
V2

- Participants in allocated study group, transitions only for CAB to TDF/FTC
- Required OLI and adherence threshold
- Required LARC
- Required pregnancy confirmation 4 weeks apart
- 48 week seroconverter schedule

V3

- Participants can choose to move from TDF/FTC
- OLI not required and therefore adherence threshold not essential for injection (but still document for interest)
- LARC not required, counsel participants about options to prevent pregnancy and knowns/unknowns re safety
- Pregnancy confirmed on two separate samples but can be done in single or more than one visit
- No seroconverters schedule; guidance from alias and protocol to confirm diagnosis and link to care

V3.0 Site Activation Requirement



Note: Each site must receive written approval from the LOC before it may implement the v3.0 protocol

Data Management Training

- Contact Stephanie Beigel-Orme (sbeigelo@scharp.org)
- She will share a recording of a previous data training for the v3.0 protocol

Scenario 1

- A participant was randomized to TDF/FTC initially, with no AE/medical contra-indications wants to move to CAB LA. What do you do?

Scenario 2

- A participant who is on CAB LA with no AE/medical contraindications wishes to stay on CAB LA. What do you do?

Scenario 3

?

- A participant seroconverted to HIV+ 8 weeks ago, under protocol v2.0. What do you do relative to protocol version 3?

Scenario 4

- A participant was on CAB LA but decides not to continue in the study. What do you do?

Scenario 5

A participant has a Grade 3 ALT in Step 4c of the OLE.

What do you do?

Scenario 6

- A participant has had the Covid-19 vaccine. What do you do?

Scenario 7

- A participant has a confirmed CrCL of less than 60 mL/min during Step 4c, Day 0. What do you do?

Scenario 8

- A participant who became pregnant under version 2.0 presents to the clinic after v3.0 has been implemented. She presents at Week 24 of pregnancy and wishes to participate in v3.0. What do you do?

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ACKNOWLEDGEMENTS

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Trial staff
Network partners
SMC, DSMB

Partners and funders

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Data Management

New Steps/Schedules

- New Steps have different visit numbers

Step Name	Treatment Regimen	Visit Numbers
Step 4a	Oral CAB	Visit 55
Step 4b	Loading Dose (4-week interval) CAB-LA	Visit 56
Step 4c	Standard Dose (8-week interval) CAB-LA or TDF/FTC	Visit 57-63 Visit 64-70
Step 4d (Sub-Study)	TDF/FTC or CAB-LA	Visit 76-94
Step 5	TDF/FTC	Visit 71-75

SDMC: OLE Data Collection Updates

- Rave database has been modified to include new OLE Steps
- CASI updates currently being updated
- More extensive training will be scheduled prior to go-live

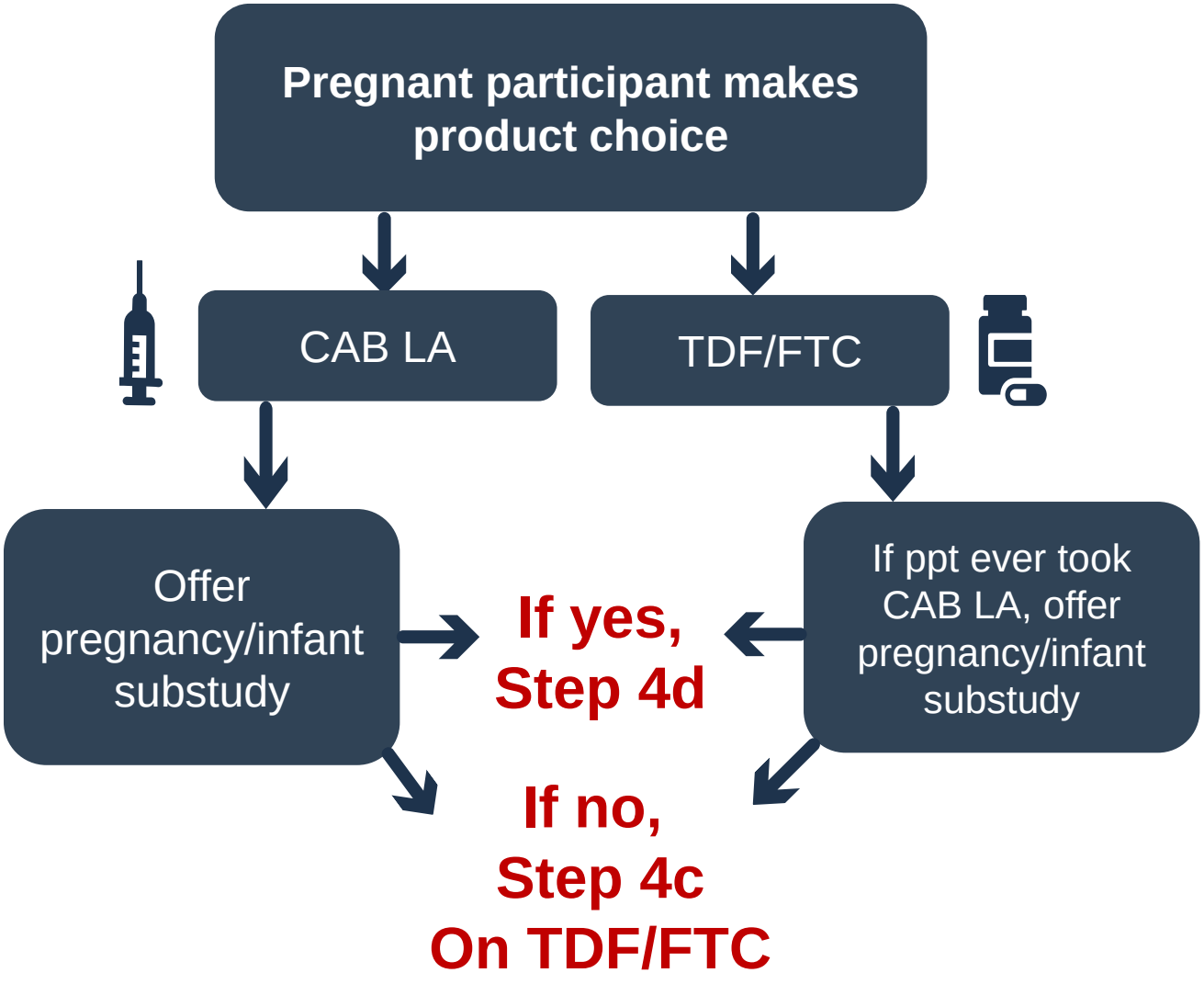
New Forms

- Product Choice - OLE
- Date of Visit - OLE
- Interim Visit Summary – OLE
- Additional Procedures – OLE
- Contraception -OLE
- Product Hold - OLE YN
- Product Hold - OLE
- Log Revisions
- Pregnancy Test Results-OLE
- Pregnancy Report-OLE

New Forms: Sub-Study

- Consent - Pregnancy Infant Sub-study
- Date of Visit - Pregnancy OLE
- Ultrasound - OLE
- Sub-study Infant PTID
- Pregnancy Outcome Log – OLE
- Infant Specimen Collection - Blood (Plasma)
- Specimen Collection - Breast Milk
- Infant Breastmilk Feeding Assessment
- Adverse Event - Infant Y/N
- Adverse Event - Infant

Management of Existing Pregnant Participants



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- No seroconverters schedule; guidance from alias and protocol to confirm diagnosis and link to care