HPTN 084: 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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Johannesburg, SA
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V1.0

HPTN 084
Long-acting Injectable For the Epidemic

Brief recap of where we are

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The Blinded Portion of the Trial

- The trial opened to Enrollment in November, 2017.
- A total of 3,224 participants were enrolled at 20 sites.
- The blinded portion of the trial was stopped by the DSMB for efficacy in November, 2020.
- Participants were unblinded to their original randomized study regimen and continued on it until the protocol amendment to offer open-label CAB LA was approved.

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Setting the Stage for v4.0

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The Open-Label Extension – first 48 weeks (OLE1)

- The OLE1 opened to Enrollment in January 2022.
- Duration is 48 weeks.
- The following Steps were added to the protocol: Steps 4 and 5.
- Participants were permitted to choose which PrEP agent they preferred (CAB LA vs. TDF/FTC) up to week 24.
- Pregnant women exposed to CAB LA at any time were eligible for Step 4d. Pregnant participants in step 4d could choose to stay on CAB or take TDF/FTC during pregnancy

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HPTN OLE objectives

- 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

HPTN OLE pregnancy objectives

Pregnant and post-partum participants **with prior or current exposure to CAB** during pregnancy:

- 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 **concentration in breastmilk and infants** among women who receive CAB LA injections during pregnancy and/or the early post-partum period.

Open-label extension - pregnancy

- 96 weeks duration (48 weeks of OLE1 and 48 weeks of OLE2)
- No requirement for LARC
  - Participants counselled about risks and benefits of CAB use in pregnancy
- Pregnancy assessment at each visit
- If test positive, option to enrol in pregnancy and infant sub-study IF
  - Prior CAB exposure (1+ injections)
  - On TDF/FTC arm but desire CAB use in pregnancy
  - Options to consent to active dosing in pregnancy
- Monthly follow up through pregnancy
  - Injections 8-weekly +/-
  - PK sample collection – trough and 4 weeks post-injection
  - ANC at visits aligned to WHO schedule, early ultrasound
- At delivery
  - Outcome assessments
  - + Sample collection including cord blood, maternal samples at delivery
- Post-partum
  - Maternal sample collection – blood, breastmilk
  - Infant sample collection – plasma
  - Outcome assessment at 48 Weeks

HPTN 084 OLE current status

- All sites activated to OLE 1 (v3.0) (week 0-48)
- 2472/2684 (92.1%) eligible participants accepted OLE
- 78.4% of participants have accepted CAB LA for PrEP
- On track to achieve pregnancy PK and short-term safety target enrollments
- Version 4 issued to sites to extend OLE follow-up to a total of 96 weeks ie. OLE2 week 56-96
  - Ward 21 has approvals and has started

HPTN 084 OLE current status- Retention

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https://atlas.scharp.org/cpas/files/HPTN/084/%40files/hptn_084_ole_report.pdf

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Prophylaxis in HIV–Uninfected Women
Atlas OLE Report – January 19, 2023
Visit Cutoff Date: January 19, 2023
Table 3A – Visit Completion by Visit and Initial OLE Regimen Choice [1]

	Overall	Initial OLE Regimen Choice TDF/FTC	Initial OLE Regimen Choice Cabotegravir
Total Participants Enrolled in OLE [2]	2472	535	1931
Step 4a – Oral CAB			
Day 0	187	0	187
Step 4b – Loading Dose CAB–LA			
Day 0/ Week 4	993	0	993
Step 4c – Standard Dose CAB–LA or TDF/FTC			
Day 0	2381	524	1857
Week 8	2259/2452 (92.1%)	471/525 (89.7%)	1788/1927 (92.8%)
Week 16	2132/2382 (89.5%)	444/522 (85.1%)	1688/1860 (90.8%)
Week 24	1755/2009 (87.4%)	354/468 (75.6%)	1401/1541 (90.9%)
Week 32	1090/1232 (88.5%)	232/294 (78.9%)	858/938 (91.5%)
Week 40	363/403 (90.1%)	64/81 (79.0%)	299/322 (92.9%)
Week 48	22/23 (95.7%)	4/5 (80.0%)	18/18 (100.0%)
Step 4d – Pregnancy and Infant Sub–Study [3]			
Day 0	65	12	53
Week 4	82/143 (57.3%) [3,4]	13/33 (39.4%)	69/109 (63.3%)
Week 8	69/77 (89.6%)	10/11 (90.9%)	59/66 (89.4%)
Week 12	54/64 (84.4%)	10/12 (83.3%)	44/52 (84.6%)
Week 16	39/52 (75.0%)	3/5 (60.0%)	36/47 (76.6%)
Week 20	27/40 (67.5%)	2/4 (50.0%)	25/36 (69.4%)
Week 24	29/40 (72.5%)	4/6 (66.7%)	25/34 (73.5%)
Week 28	18/27 (66.7%)	1/3 (33.3%)	17/24 (70.8%)
Week 32	18/24 (75.0%)	1/3 (33.3%)	17/21 (81.0%)
Week 36	15/21 (71.4%)	1/2 (50.0%)	14/19 (73.7%)
Week 40	15/19 (78.9%)	1/2 (50.0%)	14/17 (82.4%)
Post Partum			
Week 2, pp	19/53 (35.8%)	1/19 (5.3%)	18/34 (52.9%)
Week 4, pp	16/52 (30.8%)	0/19 (0.0%)	15/32 (46.9%)
Week 8, pp	12/33 (36.4%)	2/16 (12.5%)	10/17 (58.8%)
Week 16, pp	8/25 (32.0%)	1/14 (7.1%)	7/11 (63.6%)
Week 24, pp	2/9 (22.2%)	0/6 (0.0%)	2/3 (66.7%)

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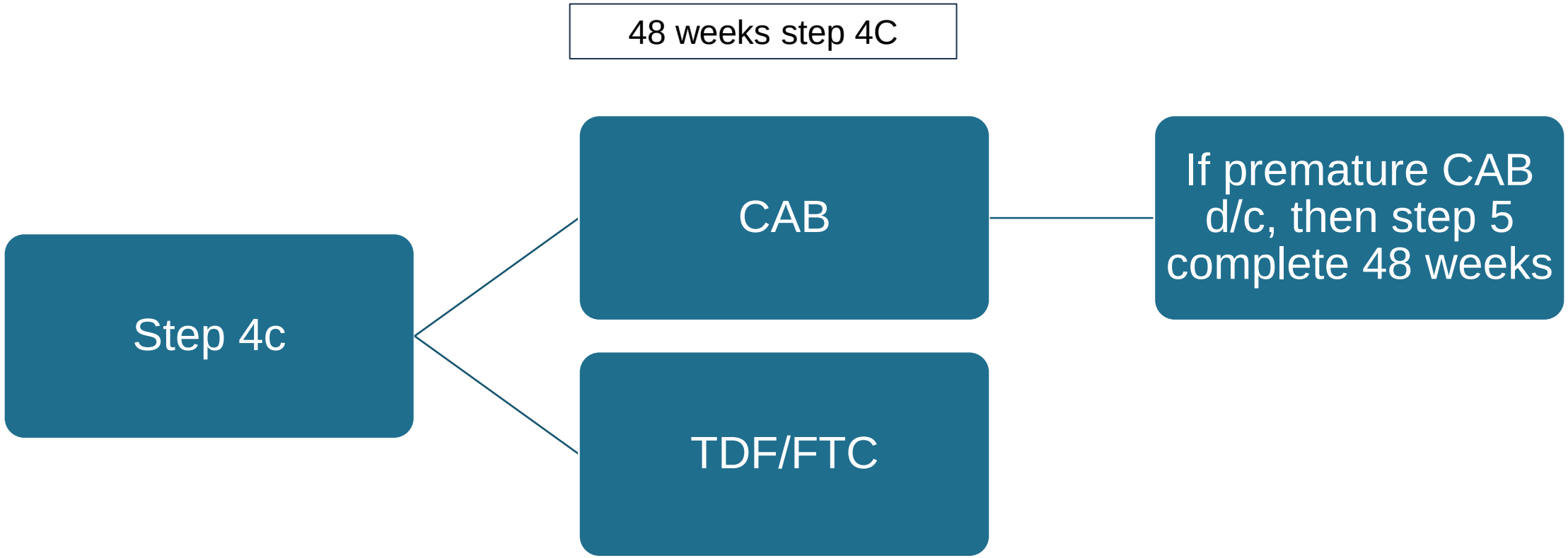
OLE 2- in a nutshell

Main intent is to extend CAB LA access to PPTs for an additional 48 weeks, follow participants who transition off of CAB LA for the duration of the PK tail, and follow pregnant women to 48 weeks post delivery. Nice summary from pp 161-2 of v4.0:

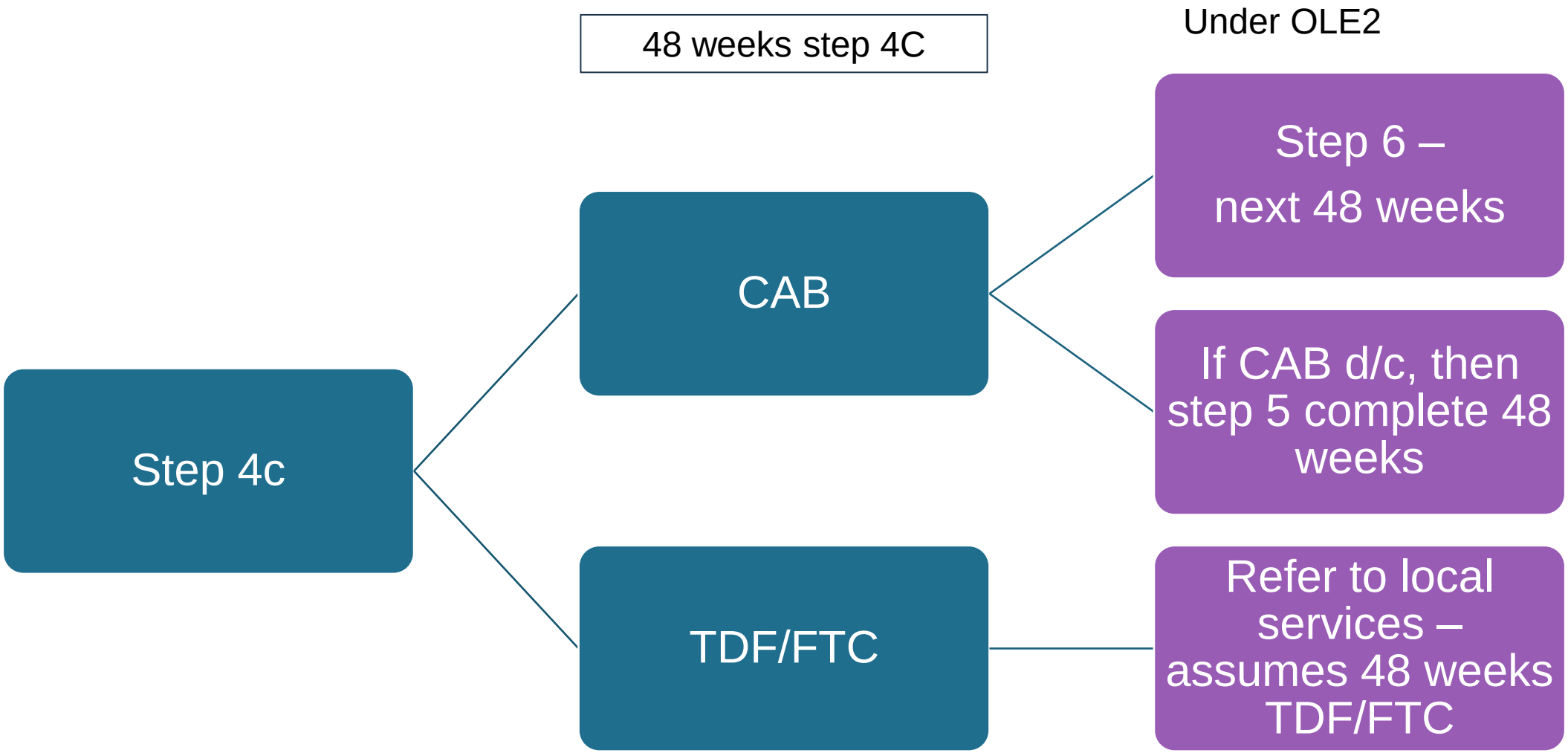
- Participants who received CAB LA in OLE1 who decline CAB LA in OLE2 (Step 6) are offered Step 5
- Those in Step 5 during OLE1 will complete Step 5 but complete follow up at week 48 of step 5
- Those receiving TDF/FTC or no product in 4c and who are not pregnant in OLE1 will end follow up at week 48 and are not offered OLE2

OLE2 transitions – non-pregnant

Under OLE1



OLE2 transitions – non-pregnant



Step 6 of OLE 2

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f. Step 6

Appendix VIII: Schedule of Evaluations for Step 6-Procedures for Participants on Maintenance Doses of CAB LA weeks 49-96

Time in Step 6 **	Week 56	Week 64	Week 72	Week 80	Week 88	Week 96
ADMINISTRATIVE PROCEDURES						
Informed Consent	X					
Locator information	X	X	X	X	X	X
Acceptability assessment			X			X
Behavioral assessment			X			X
HIV prevention counseling	X	X	X	X	X	X
Offer condoms per local SOC	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
Blood collection	X	X	X	X	X	X
Urine collection[1]	X	X	X	X	X	X
Vaginal swab collection[2]			X			X
Adherence counseling[3]	X	X	X	X	X	X
Administer CAB LA	X	X	X	X	X	X
LOCAL LABORATORY EVALUATIONS & PROCEDURES						
HIV testing[4]	X	X	X	X	X	X
HIV viral load testing[5]	X	X	X	X	X	X
Pregnancy testing, only if indicated[1]	X	X	X	X	X	X
Chemistry testing						X
Liver function testing[6]						X
Syphilis testing			X			X
GC/CT and TV testing[2]			X			X
Plasma storage[7,8]	X	X	X	X	X	X
DBS storage[8]	X	X	X	X	X	X

** Participants will flow from Step 4c into Step 6.

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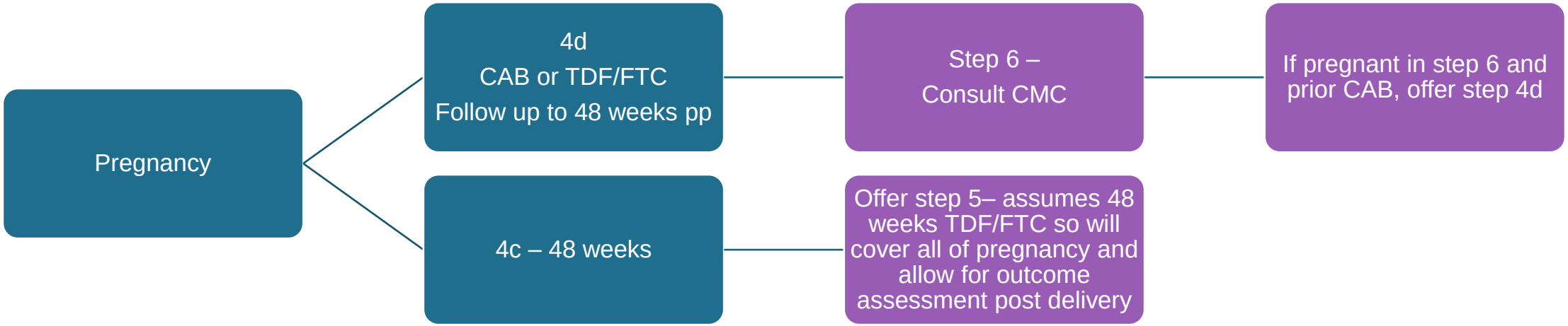
OLE 2- in a nutshell (cont.)

- Those pregnant in OLE1, Step 4d will complete the 4d visit schedule before considered for Step 6.
  - If there is a pregnancy loss they may transition to Step 6 but consult CMC first

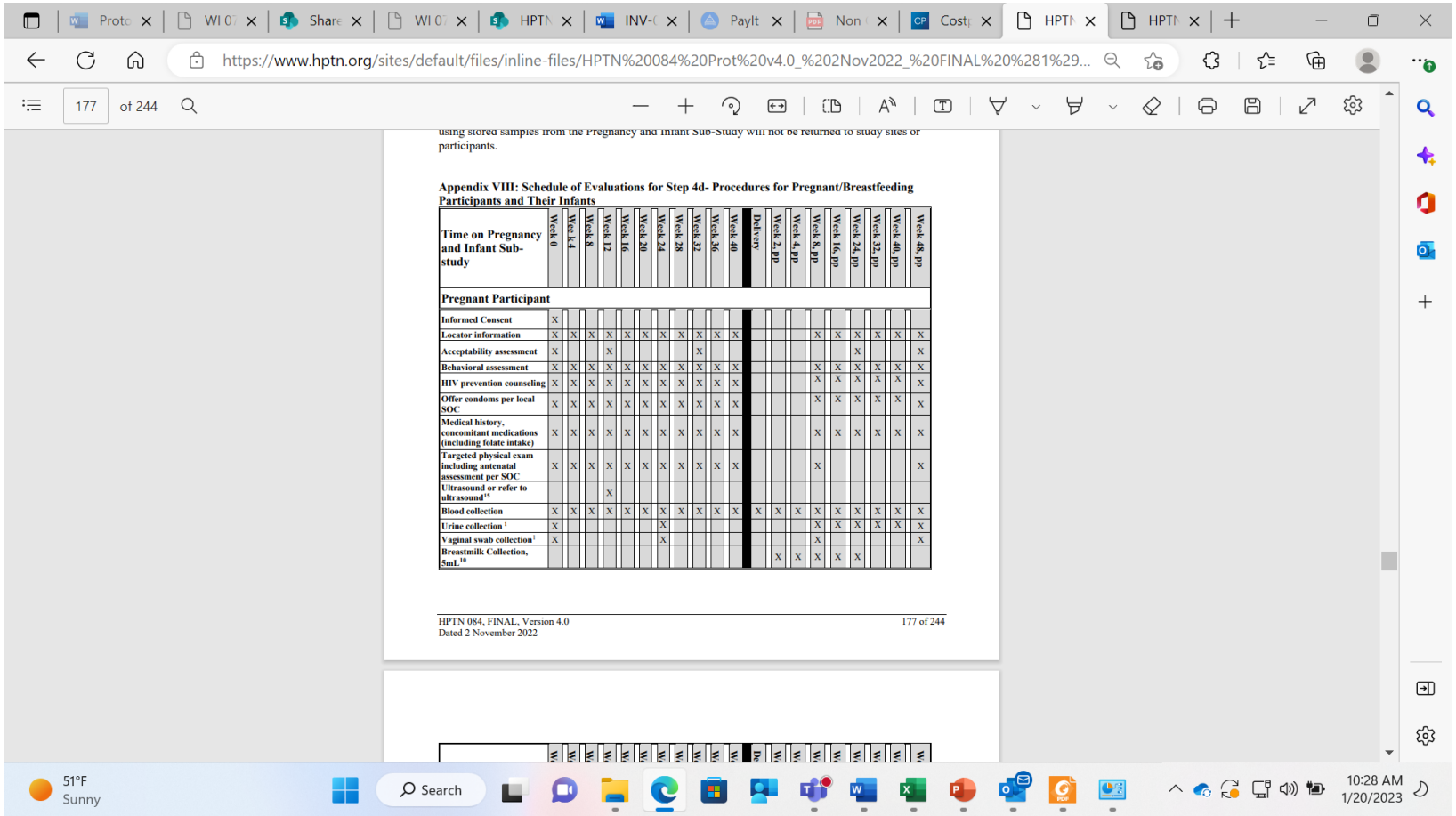
- Those who become pregnant in Step 6 and have ever received 1 CAB injection will be offered Step 4d. Anyone who declines will not receive CAB LA during pregnancy, but be followed in Step 5

- Those pregnant in OLE1 Step 4c who declined participation in the pregnancy and infant substudy (4d) will transition to Step 5 in OLE2 to ensure pregnancy outcome data and PrEP during pregnancy

OLE2 transitions –pregnant



Step 4d OLE 2 SoE



using stored samples from the Pregnancy and Infant Sub-Study will not be returned to study sites or participants.

Appendix VIII: Schedule of Evaluations for Step 4d- Procedures for Pregnant/Breastfeeding Participants and Their Infants

Time on Pregnancy and Infant Sub-study	Week 0	Week 4-4	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
Pregnant Participant																				
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[15]				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, 5mL[10]													X	X	X	X	X			

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Dated 2 November 2022

Step 4d OLE 2 SoE (con't.)

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Time on Pregnancy and Infant Sub-study	Week 0	Week 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
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	X
ISR Assessment, only for PPTs receiving CAB LA injections		X		X		X		X		X					X	X	X	X	X	X
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	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	X			
Infant																				
Pregnancy outcome assessment including abbreviated infant examination[12]															X					X
Infant feeding history															X	X	X			
Cord blood collection[17]												X								
Infant blood collection[17]												X	X	X	X	X	X	X	X	X
Infant AE assessment[18]												X	X	X	X	X	X			
Infant HIV testing, if the mother has one or more reactive/positive HIV test results [13]												X	X	X	X	X	X	X	X	X
Cord blood storage[9,14]												X								
Dried blood spot storage [9, 16]												X	X	X	X	X	X	X	X	X
Infant plasma storage[9,14]												X	X	X	X	X	X	X	X	X

NOTE: PK analysis will be performed on cord blood and infant plasma samples at an offsite laboratory.
[1] GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

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Step 5 of OLE 2 SoE

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Appendix VIII: Schedule of Evaluations for Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA discontinuation

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[1]	X	X	X	X	X
Vaginal swab collection[1]	X		X		X
Adherence counseling[2]	X	X	X	X	
Dispense pills to all participants	X	X	X	X	
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	X		X		X
GC/CT and TV testing[1]	X		X		X
Plasma storage[8,9]	X	X	X	X	X
DBS storage[9]	X	X	X	X	X

FOOTNOTES FOR Step 5, SOE

* Day 0 of Step 5 should be scheduled no later than 8 weeks after the last injection. Attempts should be made to bring the participant in earlier rather than later than the target date. See SSP Manual for further details.

[1] GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

[2] Refer to the SSP Manual.

[3] The HIV testing algorithm is provided in the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

[4] This testing will be performed for all study participants, regardless of HIV status or the results of other HIV tests. This testing must be performed with an assay with a lower limit of quantification of 50 copies/mL or lower.

[5] Pregnancy testing may be performed in the clinic or the laboratory at all visits where this testing is indicated. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower.

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OLE 2- in a nutshell (cont.)

- Once Step 6 is complete anyone who desires CAB LA will be referred to local access programs

- Those with confirmed HIV infection prior to enrollment in OLE2 will not be offered OLE2, but follow up for confirmation and linkage to care will still be required
  - May need to be reconsented if this process of confirmation or linkage to care not complete

A few reminders

- Participants who prematurely stop taking CAB LA during OLE 2 will move to Step 5. These participants will be offered TDF/FTC to cover the PK tail.
- Step 4d is for pregnant participants who have ever been exposed to CAB LA.
- To receive CAB LA during pregnancy, a participant must agree to be followed on Step 4d (**consent them prior to injection)** because it includes additional safety monitoring.
- Contact the CMC if you have any doubts.

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HIV Prevention Trials Network

- Leadership and Operations Centre, FHI360
- Laboratory Centre (Johns Hopkins)
- Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchison Cancer Research Center
- HPTN Leadership

HPTN 084 Study team

- 20 sites in 7 countries in sub-Saharan Africa
- Community advisory boards and partners

… and our study participants!

UM1AI068619-15 (HPTN Leadership and Operations Center), UM1AI068617-15 (HPTN Statistical and Data Management Center), and UM1AI068613-15 (HPTN Laboratory Center).