Letter of Amendment #3 to:

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

Version 3.0, 12 August 2021

DAIDS Document ID: 38070
IND # 122, 744

LoA #3: FINAL of 14 March 2022

Instructions to the Study Sites from the Sponsor

The following information impacts the HPTN 084 study and must be forwarded to all responsible Institutional Review Boards (IRBs)/Ethics Committees (ECs) and any other required regulatory authorities as soon as possible for their information, review and approval. This Letter of Amendment (LOA) must be approved all required regulatory authorities before implementation.

The following information may also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

The HPTN 084 protocol will be fully amended in the future and will include the modifications outlined in this LOA.

Text appearing below in highlighted **bold** will be added, and text appearing in highlighted ~~strike-through~~ will be deleted.

Summary of Revisions and Rationale

1. Revision 1: Added timepoints for infant AE collection and updated corresponding statistical language.

Implementation

Upon receiving IRB/EC approval, and approval of any other applicable regulatory entities, study sites must submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. An LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for HPTN 084.

Protocol Signature Page

HPTN 084

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I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Name of Investigator of Record	**Signature of Investigator of Record**	**Date**

All changes are to Appendix VIII: Procedures for Offering Open Label (OL) Cabotegravir- The Next Part of HPTN 084

1. **Revision 1:** Added Infant AE assessment timepoints

Revision 1, Change 1
Added language to Section 3. Description of Steps 4 and 5

At delivery, where feasible, a maternal blood sample and cord blood sample will be collected from the mother, and where feasible an infant blood sample will be collected at delivery. During the post-partum period, blood and breastmilk samples will be collected from the mother, and blood samples will be collected from the infant (see Step 4d SOE). Infant outcomes will be assessed at delivery up to approximately 12 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 12-month post-partum period.**

Revision 1, Change 2
Added separate headers for pregnant participants and infants, timepoints were added to delivery and partum (pp) Weeks for infant AE assessments and an associated footnote was added.

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	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																				

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
Infant																				
Infant AE assessment[19]												X	X	X	X	X	X			

[19] All infant AEs must be recorded. However, only Grade 2 and above AEs need to be reported into the database up to and including 24 weeks post-partum. All SAEs, including deaths and congenital anomalies, must be reported throughout Step 4d.

Revision 1, Change 3: Edits to three 3 OLE objectives in Section 7.0 SECTION 7.0 (MODIFIED FROM THE MAIN PROTOCOL)

- To evaluate the safety of open-label CAB LA with and without an oral lead-in over 48 weeks

We will tabulate all AEs with maximum grade ≥2 (←added or =) for those receiving OL CAB LA overall among those with and without an oral lead-in. Event rates and 95% robust confidence intervals will be calculated using a log-linear model for counts using log(person-time) as an offset, assuming a Poisson

distribution and using a robust variance (i.e. generalized estimating equations). OSP censoring will be used.

- To evaluate safety and infant outcomes among pregnant participants

Safety events, as described above, will be tabulated before, during and up to 24 weeks after pregnancy for women who become pregnant. Events will be reported overall and separately for women who did and did not receive CAB injections during pregnancy. Infant outcomes **at delivery and 12 months** will be tabulated and all congenital anomalies **individually** reported.

- **To evaluate safety in infants exposed to CAB LA during pregnancy**

We will tabulate all AEs with maximum grade >=2 among infants for 24 weeks following birth. AEs will be reported overall and separately for infants of women who did and did not receive CAB injections during pregnancy. Event rates and 95% robust confidence intervals will be calculated using a log-linear model for counts using log(person-time) as an offset, assuming a Poisson distribution and using a robust variance.