SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

HPTN 057

A Phase I Open Label Trial of the Safety and Pharmacokinetics of Tenofovir Disoproxil Fumarate in HIV-1 Infected Pregnant Women and their Infants
Version 1.0 / 23 May 2005

DAIDS Document ID 10143

THE AMENDED PROTOCOL IS IDENTIFIED AS:
Final Version 2.0 / 28 October 2009

IND # 72,531

Summary of Revisions and Rationale

The modifications included in this protocol amendment and the associated rationale is summarized briefly below. HPTN 057 study investigators will submit this Summary of Changes and the corresponding protocol Version 2.0 to all relevant regulatory authorities and Institutional Review Boards/Ethics Committees (IRBs/ECs) for approval. Upon completion of protocol registration procedures with the DAIDS Regulatory Compliance Center, Version 2.0 of the protocol may be implemented.

The most significant modifications included in this amendment are related to the addition of a forth cohort of mother-infant pairs with maternal intrapartum dosing of 600 mg and daily infant dosing of 6 mg/kg for 7 days. The decision to add this cohort was made after review of the pk and safety data from HPTN 057 Cohorts 1–3 and the pk and safety data from PACTG 394. These data suggest that daily infant dosing is safe and will be necessary to exceed the target trough concentration specified in the protocol. Cohort 4 will be modeled after the recently completed Cohort 3 in terms of number of mother-infant pairs (n=30), pk sampling scheme, safety and other assessments, visit schedule and duration of follow-up, with the only major difference being the change in infant dosing to daily dosing for 7 days.

Changes included in Letter of Amendment #1 to protocol version 1.0, dated 9 September 2005 and four Clarification Memoranda dated 1 May 2007, 29 November 2007, 25 February 2008, and 16 September 2008 are included for completeness; however, many of those changes do not specifically pertain to Cohort 4 but rather for the previously completed Cohorts 1-3.

The modifications are summarized as follows:

Summary of Revisions

This amendment incorporates one previously approved protocol Letter of Amendment and four Protocol Clarification Memoranda as well as the following additional protocol revisions:

- The results of PACTG 394 have been updated in the background section. PACTG 394 was a phase I study initiated in 2004 in the US to evaluate the pharmacokinetics and safety of a single dose of TDF given to mother during labor and a single dose to the infant at age 24 hours.

- The secondary objective related to viral studies has been expanded to include viral resistance studies of TDF in breastmilk as well as infant and maternal plasma. In addition to the secondary objectives the following sections were updated accordingly; Section 5.3.2 Maternal, Post Delivery and Follow-up, Section 7.5.2 Secondary Analysis, Section 9.2 Network Laboratory Specimens, and Schedule of Maternal Evaluations (Appendix IB).

- The TDF dosing regimen for mothers and infants and pk sampling schedule for Cohort 4 have been added throughout. Mothers will receive one 600 mg dose of TDF, which is the same dose used for Cohort 2 mothers, and infants will be dosed daily with TDF oral suspension from birth for 7 days. Mothers will have a pk sample taken at delivery and infants will have cord blood and serial PK samples taken after the birth, 4th and 7th doses of TDF.

- The antiretroviral regimens provided as standard of care for prevention of mother-to-child transmission in Brazil and Malawi has been updated in Section 2.3.

- The safety data from HPTN 057 Cohorts 1 -3 have been summarized in Section 2.4. There were no safety concerns identified in Cohorts 1-3.

- The PK data from Cohorts 1-3 and the rationale for adding a fourth cohort have been added to the section entitled; Pk and Safety Data From HPTN 057 Cohorts 1-3: Rationale for Cohort 4 (Section 2.4). Maternal TDF exposure was very similar with either 600 mg or 900 mg intrapartum doses and exceeded TDF exposure seen with single 300 mg doses in nonpregnant adults. The infant data show that the infants eliminated TDF nearly as fast as adults, and almost all infants in Cohorts 2 and 3 had trough TDF concentrations below 50 mg/mL, the trough concentration target for the protocol. These data suggest that maternal dosing at 600 mg is sufficient and daily infant dosing will be necessary in order to exceed the trough concentration target.

- The total study size has been changed to 110 evaluable mother/infant pairs which include 30, 20, 30 and 30 in each of the four cohorts. There is no restriction on the number of C-section deliveries for Cohort 4 as there was for Cohorts 1–3.

- The maternal and infant inclusion/exclusion criteria for Cohort 4 are the same as for Cohort 3 with the exception of the maternal exclusion due to the use of atazanavir or

lopinavir/ritonavir (Kaletra®) within 2 weeks of anticipated delivery. Section 3.6 Co-Enrollment guidelines has also been updated accordingly.

- Instructions for further pk sampling and dosing for Cohort 4 in instances when an infant and/or mothers dose is missed or if a mother vomits a dose have been added to Section 4.2 and are consistent with Cohorts 1-3.
- Instructions for pk sampling and re-dosing in instances when an infant vomits TDF have been added to Sections 4.2 and 5.7 and vary depending on whether or not the dose is given a day that pk sampling is scheduled.
- The TDF tablets will be supplied in bottles for Cohort 4 rather than blister packs as was used for Cohorts 1 and 3; this is specified in Section 4.3.
- For consistency with the grading parameters for calcium that were used for Cohorts 1–3, the parameters from the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse which were in effect during follow-up of Cohorts 1–3 and which include correction for albumin have been specified in the protocol for Cohort 4 as an exception to the recently issued clarification to the DAIDS Grading Table (which includes different parameters for grading calcium). This has been added to Section 4.6 Toxicity Management and Grading.
- The procedures for Cohort 4 infants will be the same as those for the previous cohorts with the following exception, infants in Cohort 4 will not have x-rays done. Because the X-rays were difficult to interpret and were of limited value in assessing TDF bone toxicity, wrist and spine x rays will not be performed on the Cohort 4 infants. The rationale for excluding the X-rays and X-ray data from Cohorts 1–3 has been added in Section 5.5.1. The protocol has been modified throughout to indicate the x-rays will only be done in Cohorts 1 – 3.
- The criteria for discontinuing PK sampling in Cohort 4 have been added to Section 5.7 and are consistent with Cohorts 1-3.
- Two new sample informed consent forms for Screening and Enrollment for Cohort 4 have been added.
- The Protocol Team Roster was updated to include appointment of a new Protocol Co-Chair, Protocol Pharmacist, NIAID and NICHD Medical Officers and removal of deceased members.
- The specific sites that are participating were added to the Schema.
- The maximum number of c-section deliveries for Cohorts 1 and 3 was clarified to state that the maximum number is 7 per country rather than per site.
- The changes included in the previously issued LoA and Clarification Memoranda are also included.
- The DAIDS Document ID and IND numbers were added to the face page.

- The Study Sponsor was updated to International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT). The Study Monitoring Section (10.3) was updated to include IMPAACT as well as HPTN. The Use of Information and Publications Section 10.6 was modified to state that IMPAACT policies will be followed instead of HPTN policies.

- The reference numbers throughout the protocol were updated to accommodate additional references.

- Other minor editorial and typographical updates and corrections were made throughout.