Letter of Amendment # 1 to:

HPTN 077: A Phase IIa Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, GSK1265744, in HIV-uninfected Men and Women, Version 3.0, October 13, 2015, DAIDS Document ID: 11964
IND # 122,744

Final Version of LoA # 1: July 6, 2016

The following information impacts the HPTN 077 study and must be forwarded to all responsible Institutional Review Boards (IRBs)/Ethics Committees (ECs) as soon as possible for their information and review. This Letter of Amendment (LoA) must be approved by all responsible IRBs/ECs, as well as other regulatory entities as applicable and per the policies and procedures of the regulatory entities.

Some of the information contained in this LoA impacts the sample informed consent. Your IRB/EC will be responsible for determining the process of informing participants of the contents of this LoA.

Upon receiving final IRB/EC and any other applicable regulatory entity approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

If the HPTN 077 protocol is fully amended in the future, this Letter of Amendment will be incorporated into the next version. Text appearing below in highlighted **bold** will be added and text with a highlighted ~~strike-through~~ will be deleted.

Summary of Revisions and Rationale

Revision 1: Dr. Adeola Adeyeye has been added to the protocol team roster. Dr. Adeyeye is the Division of AIDS Medical Officers for the study. Dr. Vanessa Elharrar has been removed from the protocol roster as she is no longer employed at the Division of AIDS.

Revisions 2a and b: The background section and sample informed consent form are updated to include a case of ALT elevation from HPTN 077, which is included in the current Investigator's Brochure (Version 5.0, dated January 6, 2016). Elevations had previously only been seen in HIV-infected participants, and this case occurred in an HIV-uninfected participant. The language is modified to this effect, but intentionally removes absolute counts of cases, in anticipation that additional cases may occur.

IMPLEMENTATION

Revision 1 **Protocol Team Roster**

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Revision 2a Section 1.4: Clinical Experience to Date – GSK1265744

The text under the "Hepatic Safety" subsection of section 1.4 is depicted here:

As part of the early phase development of GSK 1265744, two participants in the HIV Treatment Phase IIb LAI116482 (LATTE) study developed Grade 4 transaminase elevations. Both were HIV-infected, had pre-existing steatohepatitis, and had Grade 1 ALT/AST elevations at screening/entry. Both were treated with ABC/3TC + 744 60 mg PO QD as part of "induction therapy" in the LATTE-1 study. Laboratory assessments at week 2, and again at week 4 (for one of the two) were normal. One participant at Week 4, and the other at Week 8 (day 57) demonstrated ALT elevations 12x ULN and 8x ULN respectively. Bilirubin remained normal, as did coagulation parameters, and the participants were clinically asymptomatic. Oral 744 was withdrawn and ALT/AST returned to normal 5 and 8 weeks thereafter, respectively.

A third participant in the HIV Treatment Phase 2b 200056 (LATTE-2) study developed Grade 4 transaminase elevations, and also > Grade 2 bilirubin elevation. This participant was HIV/HCV co-infected, with portal hypertension and Grade 3-4 fibrosis on Fibroscan but normal screening transaminase levels. He was begun on ABC/3TC (600 mg/300 mg) + 744 30 mg PO QD. On Day 35 of treatment the participant developed ALT 5 x ULN, which peaked one week later at 7 x ULN. Drug was withdrawn and the ALT/AST and bilirubin have normalized. The participant was clinically asymptomatic. A fourth participant receiving 744 30 mg PO + ABC/3TC developed an ALT >5x ULN after approximately one year on therapy which lead to discontinuation of oral therapy, with resolution of ALT values. Initial ALT elevations were detected approximately 6

months after initiating therapy. This participant was noted to have steatohepatitis on ultrasound imaging and did not develop evidence of hepatic dysfunction. Oral 744 could not be ruled out as a contributing factor to the observed liver injury.

A participant in HPTN 077 without known pre-existing liver disease, and without HIV-infection developed Grade 3 ALT elevation after 12 weeks of injectable CAB LA or placebo treatment; the participant was asymptomatic, and ALT returned to normal 15 weeks after withdrawal of study product. A serologic and ultrasonographic evaluation did not reveal alternative etiology for the ALT elevation; no biopsy was performed.

Revision 2b APPENDIX XII: SAMPLE SCREENING AND ENROLLMENT INFORMED CONSENT FORM FOR PARTICIPANTS ENROLLING UNDER VERSION 3.0

The relevant text included under "RISKS AND/OR DISCOMFORTS" is depicted here:

Study Medications

The drug being used in this study is currently being used in other people participating in similar studies. Those studies have reported side effects of the study drug, such as headaches, dizziness, upset stomach, rash, liver problems, fatigue, or injection site reaction (pain, irritation, skin redness, bumps, swelling, itching, bruising). Other reported side effects were nausea, stomach cramps, constipation, and right hand pain.

There have been some people who were taking this medicine ~~in other studies~~ who have had liver side effects. ~~All~~ **Some** of these people were HIV-infected (HIV positive) and ~~they all had~~ some **had** damage to their liver before taking the GSK 744 study medication. ~~In those studies, w~~**W**hile taking the study medication, their blood tests showed that their liver was irritated, although they felt well. The medications were stopped, and the liver blood tests ~~are~~ **returned to** normal. In HPTN 077, anyone with HIV-infection, Hepatitis C (or B), or any liver irritation will not be allowed to be in the study.