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LETTER OF AMENDMENT

DATE: October 23, 2020

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5324 Protocol Team

SUBJECT: Letter of Amendment #4 for Protocol A5324

The following information affects the A5324 study and must be forwarded to each site's institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by the IRB/EC before implementation.

The following information may also affect the Sample Informed Consent. The site IRB/EC is 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 approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An 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 file.

This LOA is being implemented for the following reasons:

- To update the protocol team roster.
- To incorporate the instructions for alternate study product dispensing and completion of post-entry evaluations that were provided through A5324 Version 2.0 Clarification Memo (CM) #3 for participant and site staff safety and flexibility to complete study visits during the ongoing COVID-19 pandemic.
- To update the sample informed consent (SIC) to include information for participants about adjustments that may be made to their study visits during the ongoing COVID-19 pandemic.

The following are changes (noted in bold or strikethrough) to A5324, Version 2.0, 08/25/20, titled "A Randomized, Double-Blinded, Placebo-Controlled Trial Comparing Antiretroviral Intensification with Maraviroc and Dolutegravir with No Intensification or Intensification with Dolutegravir Alone for the Treatment of Cognitive Impairment in HIV." These changes will be included in the next version of the A5324 protocol if it is amended at a future date. Changes that have already been made (either by LOA or by CM) have been incorporated in the excerpted text shown below (and are no longer presented in bold or strikethrough).

1. A Protocol Signature Page (PSP) is appended for submission to DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

2. In the Protocol Team Roster, the following updates have been made:

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3. In section 5.1.2, Administration and Dispensing, the following paragraph has been added as the last paragraph in this section, below item number 5.1.2.2:

   For rare instances or emergency cases, the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* permits shipment by mail or courier of study product from the site directly to participants. This method should only be used on a short-term basis and if permissible by the site's institution. If this method is to be implemented, each site's Pharmacist of Record (PoR) must develop appropriate procedures for the shipment or courier of study product to identified participants in accordance with these guidelines, and document chain of custody. Prior to implementation, the site PoR must coordinate with site clinic staff to determine the appropriateness of this method for applicable protocols and participants.

4. In section 6.1, Schedule of Evaluations, the visit window for weeks 36 to 96 has been changed as shown below:

Evaluation	Screening	Pre-Entry	Entry	Post-Entry Evaluations (Weeks)										Confirmation of VF	Premature Study/Treatment Discontinuation
				2	4	12	24	36	48	60	72	84	96		
Visit Windows				± 1 wk		± 2 wks		- 4 wks, + ~~8~~ **12** wks							

5. In section 6.2.3, Post-Entry Evaluations, the following instructions have been added to the On-Treatment Evaluations subsection:

   Alternate Completion of Post-Entry Evaluations

   - **If the participant's visit is postponed within the extended visit window, the site should ensure that the participant has sufficient supply of the study products to last him or her to the point when he or she can come to the clinic.**
   - **If the participant does not have enough supply of study products to allow the visit to be postponed, the site must attempt to contact the participant by phone or other method available.**
     - **During the remote contact for visit week 72 or week 96, the site should conduct a safety follow-up (such as inquiring about signs and symptoms) to determine if any AEs or serious adverse events (SAEs) have occurred since the last visit and if the participant needs medical follow-up. Additionally, the site should complete the questionnaires and adherence assessment per section 6.3.9, section 6.3.10, and MOPS section 4. All other evaluations and stored samples that will be missing for the visits, and the reason why they are missing, must be documented in the participant's study file.**
     - **At all visits except week 96, the site should confirm if the participant is able to**

receive a new supply of study medications if it is shipped via mail or sent via courier (see section 5.1.2). If a participant is unable to pick up or receive study medications via shipment or courier, the site should consult the study core team (actg.corea5324@fstrf.org) for further guidance.

- **If safety laboratory evaluations, and a pregnancy test for female participants of reproductive potential, cannot be performed, the continuation of study treatment is at the discretion of the Investigator of Record (IoR). The site should inform the study core team of the decision of the IoR.**

6. In section 6.2.4, Discontinuation Evaluations, the following instructions have been added to the Premature Treatment Discontinuation Evaluations subsection:

Alternate Completion of Post-Entry Evaluations

- **The visit can be postponed within the extended visit window if needed to safely conduct a face-to-face clinic visit. If the participant can safely be seen in the clinic, the site should perform all the evaluations for the visit per the SOE in section 6.1, Letter of Amendment (LOA) #1, and LOA #2.**
- **If the visit cannot be completed with a face-to-face visit despite the extended visit window, the site must attempt to contact the participant by phone or other method available. During the remote contact for visit week 72 or week 96, the site should conduct a safety follow-up (such as inquiring about signs and symptoms) to determine if any AEs or SAEs have occurred since the last visit and the participant needs medical follow-up. Additionally, the site should complete the questionnaires and adherence assessment per section 6.3.9, section 6.3.10, and MOPS section 4. All other evaluations and stored samples that will be missing for the visits, and the reason why they are missing, must be documented in the participant's study file.**

7. In Appendix I, Sample Informed Consent (SIC), the following has been added as a new subsection, before the Optional Lumbar Puncture subsection, in the section WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?:

COVID-19 Pandemic Considerations
During the ongoing COVID-19 pandemic, the following adjustments may be made to your study visits:

- **If there is an outbreak of COVID-19 in your community and you are unable to come to the study clinic, your study doctor or staff member will try to contact you by phone or other remote method if you have a study visit due. During this contact:**
  - **You will be asked about your health since your last study visit or contact.**
  - **If there are questionnaires to be completed for a particular study visit, you will be asked some questions about how you are feeling, how well you are able to perform your daily activities, your alcohol and drug use, and how well you are taking your current anti-HIV drugs.**
  - **If you did not have to stop taking the study medications early:**
    - **You will be asked if you are able to pick up your new supply of study medications from the study clinic. If you are not able to pick up the study medications, you will be asked if you can receive the study medications through the mail or a courier. You and your study doctor or staff member will decide on the best way to make sure you receive your new supply of study medications.**
    - **Your study doctor or staff member will inform you if you can continue taking the study medications.**

A Randomized, Double-Blinded, Placebo-Controlled Trial Comparing Antiretroviral Intensification with Maraviroc and Dolutegravir with No Intensification or Intensification with Dolutegravir Alone for the Treatment of Cognitive Impairment in HIV

SIGNATURE PAGE

I will conduct the 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.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title