ACTG Network Coordinating Center

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LETTER OF AMENDMENT

DATE: March 29, 2018

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

FROM: A5324 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5324, Version 2.0, 08/25/17, entitled "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"

The following information impacts the A5324 study and must be forwarded to your 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 your IRB/EC before implementation.

The following information may also impact the Sample Informed Consent. Your 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 files.

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The specific updates that are being made via this LOA #1 to A5324, Version 2.0, 08/25/17, are listed below. An italicized statement provides the location of the update within the identified section of the protocol. New text resulting from this LOA appears in **bold**; deleted text is shown in ~~strikethrough~~. Changes that were made in the excerpted text shown below when the protocol was amended to Version 2.0 are no longer presented in bold.

1. Section 5.1.2

   The paragraph below is being added as the second paragraph in this section.

   At study entry, dispense either a 12-week supply of study medication or a sufficient quantity to last until the participant's next visit. Refer to section 6.3.11 for the study medication dispensing schedule.

2. Section 6.1

   In this section, Stored Plasma is being deleted from the Confirmation of VF visit 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		
Stored Plasma		X	X	X	X	X	X		X		X		X	~~X~~	X

3. Section 6.2.4

   In this section, the <u>Premature Treatment Discontinuation Evaluations</u> sub-section is being updated as shown below.

   <u>Premature Treatment Discontinuation Evaluations</u>
   Participants who discontinue the study medications before the end of the study should have the premature treatment discontinuation evaluations done within 14 days after stopping study medications. Participants will be followed off study treatment/on study. They should be encouraged to continue to attend all study visits and receive study evaluations as per section 6.1, with the exception of the ~~adherence questionnaires~~ **PK studies**, and optional lumbar puncture, through completion of the study.

4. Section 6.3

   The first paragraph in this section is being updated as shown below.

   All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document:
   ~~https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf~~
   https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf.

5. Section 6.3.5

   In this section, height measurement at week 12 is being removed from the Targeted Physical Exam sub-section.

   Targeted Physical Exam
   After screening, a targeted physical examination, including height (at entry ~~and week 12~~ only), weight, and vital signs (temperature, pulse, and blood pressure) should be per section 6.1, along with additional assessments based upon previously identified findings, diagnoses, or new signs or symptoms since the last visit.

6. Section 6.3.11

   This section is being updated as shown below.

   At study entry ~~and thereafter~~, **dispense either a 12-week supply of study medication or a sufficient quantity to last until the participant's next visit. Beginning with the week 12 visit,** study medications will be dispensed every 12 weeks. At weeks 36, 60, and 84, participants will return for study medication dispensing only. No other study evaluations will be performed.

7. Section 6.3.15

   In this section, the second paragraph in the Plasma sub-section is being deleted.

   Plasma
   Plasma will be collected and stored for single copy assay (SCA).

   ~~Plasma collected at the confirmation of VF visit will be stored for resistance and tropism testing if VF is confirmed (see sections 6.3.19 and 6.3.20).~~

8. Section 10.2.1

   In this section, the sentence below is being added to the end of the first paragraph.

   The last three doses of study medication taken before the PK sample collection will be recorded on the CRF.

9. Section 10.2.2

   In this section, the sentence below is being added to the end of the first paragraph.

   The last three doses of study medication taken before the trough sample collection will be recorded on the CRF.

10. Section 11.3.2

This section is being updated as shown below.

The site investigator will make study documents (eg, consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB/EC, the site monitors, the FDA, the NIAID, the OHRP, ~~and~~ the industry supporter**(**s**)** or designee**, and other local, US, and international regulatory entities** for confirmation of the study data.

11. Section 12.2

This section is being updated as shown below.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain **participant** confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the **participant**, except as necessary for monitoring by the ACTG, IRB/EC, **FDA,** NIAID, OHRP, other ~~government agencies~~ **local, US, or international regulatory authorities** as part of their duties, or the industry supporter**(s)** or designee.

12. Sample Informed Consent, WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

In this section, the first paragraph in the Virologic Failure sub-section is being updated as shown below.

You will be tested for virologic failure at weeks 12, 24, 48, 72, and 96. Virologic failure is when your anti-HIV drugs are not fully suppressing HIV in the blood. If the study staff sees that your viral load has gone up, you will be asked to have another viral load test done within 30 days. About 2 teaspoons (10mL) of blood will be drawn for the viral load test. We will also draw ~~an additional 1-2~~ **about 4** teaspoons **(20mL)** ~~(6mL)~~ of blood that will be used for tests that check which anti-HIV drugs have stopped working on the HIV in your blood (resistance test) and if a specific type of anti-HIV drug will be able to control your HIV (tropism test) if the repeat viral load test shows that your viral load is still up. We will also ask you to fill out a questionnaire about how well you are taking your current anti-HIV drugs.

13. Sample Informed Consent, WHAT ARE THE RISKS OF THE STUDY?

In this section, the list of other side effects of dolutegravir (DTG) under the Risks of DTG (Tivicay) sub-section is being updated as shown below.

Other side effects of DTG include:

- Changes in liver test results, more common in people with hepatitis B or C
- Trouble sleeping
- **Abnormal dreams**
- Tiredness

- Headache
- **Anxiety**
- **Dizziness**
- **Abdominal pain**
- **Flatulence**
- **Nausea, vomiting**
- **Muscle and joint aches**

14. Sample Informed Consent, WHAT ABOUT CONFIDENTIALITY?

The following updates are being made in this section:

a. *The second paragraph in the <u>For Sites in the US</u> sub-section is being updated as shown below.*

People who may review your records include the ACTG, **U.S.** Office for Human Research Protections **(OHRP)** ~~or other government agencies as part of their duties~~, **U.S.** Food and Drug Administration (FDA), **or other local, U.S., and international regulatory entities as part of their duties,** (insert name of site) Institutional Review Board (a group that protects the rights and well-being of people in research), National Institutes of Health (NIH), study staff, study monitors, the drug company supporting this study, and its designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

b. *The second paragraph in the <u>For Sites outside the US</u> sub-section is being updated as shown below.*

Your records may be reviewed by the ACTG, **U.S. Office for Human Research Protections (**OHRP**)**, **U.S. Food and Drug Administration (**FDA**), or other local, U.S., and international regulatory entities as part of their duties**, (insert name of site) ~~IRB~~ **Institutional Review Board or Ethics Committee (a committee that protects the rights and safety of participants in research)**, National Institutes of Health (NIH), study staff, study monitors, and drug company supporting this study**, and their designees**.

15. Protocol Signature Page

Per a new regulatory requirement by the Division of AIDS (DAIDS), a Protocol Signature Page (PSP) is appended for submission to the DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

The information above will be incorporated into the next protocol version as necessary if the protocol is amended.

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
Version 2.0, 08/25/17

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 U.S. 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