ACTG Network Coordinating Center

Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910

Telephone: 301-628-3000
Fax: 301-628-3302

LETTER OF AMENDMENT

DATE: June 4, 2018

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

FROM: A5324 Protocol Team

SUBJECT: Letter of Amendment #2 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. To eliminate apparent immediate hazards to study participants, this LOA may be implemented before receiving your IRB/EC approval.

The following information also impacts the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

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.

The World Health Organization (WHO), U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMA) released a safety announcement on May 18, 2018, regarding a recent unplanned analysis of an ongoing study in Botswana of pregnant HIV-positive women on antiretroviral therapy. In that analysis, investigators noted 4 neural tube defects in infants born to 426 women who conceived while on dolutegravir (0.9%). This was compared with 0.1% of infants (14 of 11,173) treated with other antiretroviral agents. This has prompted regulatory agencies and the WHO to issue advice to health care professionals and

HIV-positive patients that includes avoiding dolutegravir in HIV-positive women who are contemplating pregnancy, testing for pregnancy prior to starting dolutegravir, and ensuring adequate birth control use among women taking dolutegravir. Based on discussions within the U.S. Division of AIDS (DAIDS) and regulatory groups, changes to the A5324 study are needed to revise the pregnancy/contraception language for HIV-infected women of reproductive potential who receive study treatment. It should be noted that enrollment of HIV-infected women of reproductive potential is permissible as long as the pregnancy/contraception inclusion criteria of the protocol are met. Of note, birth control is already required of all females of reproductive potential who participate in the trial.

The main reasons for this LOA are to update the pregnancy/contraception requirements and dolutegravir risk information in the protocol and the sample informed consent form.

TABLE OF CONTENTS

The specific updates that are being made via this LOA #2 to A5324, Final 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 and in LOA #1 are no longer presented in bold.

1. Section 2.1, Background/Rationale

   The following has been added as the last paragraph in the DTG (Tivicay) sub-section:

   In May 2018, ViiV Healthcare became aware of a potential safety issue related to neural tube defects (NTDs) in infants born to women with exposure to dolutegravir at the time of conception that was identified from a preliminary unscheduled analysis of a study conducted among pregnant women in Botswana (Tsepamo study, 4 NTDs among 426 pregnancies on dolutegravir). This represented an incidence of about 0.9% with an expected background rate of about 0.1%. In the reproductive toxicology studies, including embryo-fetal development studies performed in animals prior to drug licensure, there were no adverse development outcomes, including NTDs, but dolutegravir was found to cross the placenta. Up to now, data from the Antiretroviral Pregnancy Registry (APR), clinical trials, and postmarketing use have not indicated a potential safety issue, but data from these sources are limited. The FDA recommends that women of childbearing potential have a pregnancy test before starting dolutegravir, and that women of childbearing age who decide to take a dolutegravir-containing regimen consistently use effective contraception while on HIV treatment (www.fda.gov).

2. Section 4.1.9

   The following changes have been made to the list of acceptable forms of contraception:

   Females of reproductive potential must agree not to participate in the conception process (i**.**e**.**, active attempt to become pregnant, in vitro fertilization), and if participating in sexual activity that could lead to pregnancy, must use at least one reliable form of contraception. Female participants must use contraceptives while receiving study treatment and for 6 weeks after stopping study treatment.

   Acceptable forms of contraception include:

   - ~~Condoms (male or female) with or without a spermicidal agent~~
   - ~~Diaphragm or cervical cap with spermicide~~
   - Intrauterine device (IUD) **or intrauterine system**
   - Hormonal contraceptive **(contraceptive subdermal implant, combined estrogen and progestogen oral contraceptive, injectable progestogen, contraceptive vaginal ring, and percutaneous contraceptive patches)**

Females who are not of reproductive potential or whose male partner(s) has documented azoospermia are not required to use contraceptives. Any statement of self-reported sterility or that of her partner's must be entered in the source documents.

NOTE: Acceptable documentation of lack of reproductive potential is oral or written documentation from the participant.

3. Section 6.1, Schedule of Evaluations

The schedule of pregnancy testing has been changed to:

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		
Pregnancy Testing	X		X	~~Whenever pregnancy is suspected~~											~~If pregnancy is suspected~~
				X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**

4. Section 6.2.2, Entry Evaluations

The following change has been made to this section:

Entry evaluations must occur at least 24 hours after pre-entry unless otherwise specified. Participant must begin treatment within 3 days after randomization. **Refer to section 6.3.12 Laboratory Evaluations, <u>Pregnancy Test</u> sub-section, for the pregnancy test requirement for females of reproductive potential if treatment cannot be started on the same day as randomization.**

5. Section 6.2.4, Discontinuation Evaluations

The following paragraph has been added as the last paragraph in the <u>Premature Treatment Discontinuation Evaluations</u> sub-section:

Refer to section 7.3 Pregnancy, <u>Pregnancy Outcomes and Reporting</u> sub-section, for additional guidance for monitoring women who become pregnant while on study and prematurely discontinue study treatment.

6. Section 6.3.11, Study Medication Dispensing

The following change has been made to 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. 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 6.3.12, Laboratory Evaluations

   The following changes have been made to the second paragraph in the Pregnancy Test sub-section:

   Negative pregnancy test must be obtained within 48 hours prior to ~~study entry~~ **randomization** for females of reproductive potential as defined in section 4.1.8. **If study treatment cannot be started within 72 hours of obtaining the negative pregnancy test for randomization, a repeat test must be performed and must be negative before starting treatment.** ~~After entry, perform a pregnancy test when pregnancy is suspected. Refer to section 7.3 for pregnancy and pregnancy outcome reporting requirements.~~

   After entry, perform a pregnancy test in females of reproductive potential as indicated in section 6.1. Refer to section 7.3 for pregnancy and pregnancy outcomes reporting requirements.

8. Section 7.3, Pregnancy

   The following changes have been made to the first paragraph in the Pregnancy Outcomes and Reporting sub-section:

   The core team (actg.corea5324@fstrf.org) should be notified immediately if a participant becomes pregnant after study entry. Study medications must be discontinued and the underlying ART regimen continued at the discretion of the site investigator. Participants will come in for a premature treatment discontinuation evaluation visit within 14 days after stopping study medications. Participants ~~who choose~~ **should be encouraged** to stay on study ~~will continue to be followed~~ **for** on study/off study treatment **follow-up visits**, but will not have blood drawn for PK studies and stored plasma/PBMCs. They also will not have to complete the adherence questionnaire. **The investigator must ensure that participants are referred and enrolled into appropriate obstetrical care.**

9. Section 8.1, Premature Treatment Discontinuation

   The following has been added to the criteria for premature treatment discontinuation (inserted as second and third bullets in this section):

   - **Actively trying to get pregnant**
   - **Female participant of reproductive potential refuses to use one of the required contraception methods while on study treatment**

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

    The following change has been made to the last paragraph in the <u>At Study Entry Visit</u> sub-section:

    > You will continue taking the anti-HIV drugs that you are currently taking. You will also be given a combination of MVC, DTG or placebo based on the group that you are randomly assigned to. You must start the new medications within three days after you are randomized. **If you will start taking the new medications after the day you are randomized, you may need another pregnancy test before starting. If you are pregnant you cannot start the new medications.**

    The following changes have been made to the second to the last paragraph in the <u>After Entry</u> sub-section:

    > At weeks 36, 60, and 84, you will return for refill of your study drugs. **If you are a woman and able to become pregnant, you will also have a pregnancy test.** These ~~refills~~ **visits** should take about 30 minutes or less. ~~No other evaluations will be done.~~

11. Appendix I, Sample Informed Consent, 'WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?'

    The following addition has been made to the reasons the study doctor may take a participant off the study drugs without permission of the participant:

    > The study doctor may need to take you off the study drugs without your permission if:
    > - you become pregnant or start breastfeeding
    > - **you decide that you want to become pregnant or actively try to get pregnant**
    > - **you do not want to use one of the required birth control methods while on the study treatment**
    > - continuing the study drug(s) may be harmful to you
    > - you need a treatment that you may not take while on the study
    > - you are not able to take the study drug(s) as required by the study

12. Appendix I, Sample Informed Consent, 'WHAT ARE THE RISKS OF THE STUDY?'

    The following changes have been made to this section:

    > The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects **with a known or possible relationship**. **It is very important that you tell your study doctor of any changes in your medical condition while taking part in the study.** If you have questions concerning the additional study drug side effects please ask the medical staff at your site. **At any time during the study, if you believe you are experiencing any of these side effects, you have the right to ask questions on possible and/or known risks.**

There is a risk of serious and/or life-threatening side effects when non-study drugs are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all drugs you are taking (including non-prescription drugs, vitamins and herbal supplements) before you start the study and **you must ask for approval for taking** ~~also before starting~~ any new drugs while **you are** on the study. You must also tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

The following changes have been made to the Risks of DTG (Tivicay) sub-section:

The following serious side effects have been associated with the use of DTG. These include allergic **(hypersensitivity)** reactions and liver problems, which may be life-threatening.

Contact the study doctor or your healthcare provider right away if you develop a rash while taking DTG, especially if it is associated with any of the symptoms listed below**, which could be signs of an allergic reaction**. Stop taking DTG and get medical help right away if you develop a rash with any of the following signs or symptoms:

- Fever
- ~~Generally~~ **General** ill feeling
- Extreme tiredness
- Muscle or joint aches
- Blisters or sores in mouth
- Blisters or peeling of the skin
- Redness or swelling of the eyes
- Swelling of the mouth, face, lips, or tongue
- Problems breathing

Contact the study doctor or your healthcare provider if you have any of the following symptoms that could be signs of liver problems:

- Yellowing of the skin or whites of the eyes **(jaundice)**
- Dark or tea-colored urine
- Pale-colored stools or bowel movements
- Nausea or vomiting
- Loss of appetite
- Pain, aching, or tenderness on the right side below the ribs
- **Changes in liver test results, more common in people with hepatitis B or C**

People with a pre-existing history of depression or other mental health illness may be at greater risk for suicidal thoughts, or attempts, which may lead to death. If your mental health illness worsens, or if you develop suicidal thoughts, call the study doctor or your healthcare provider right away.

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 **(fear, worry)**
- Dizziness
- Abdominal pain
- Flatulence **(gas in the abdomen)**
- Nausea/Vomiting
- Muscle and joint aches

Dolutegravir and Pregnancy:
Early results from a large study in Botswana of pregnant women showed a possible increased risk of certain types of serious birth defects involving the brain and spinal cord in babies born to women who received DTG for HIV treatment at the time of becoming pregnant or early in their pregnancy. No cases of babies born with these types of birth defects have been reported among women who started DTG later in pregnancy.

Tell the study doctor or your healthcare provider about any side effect that bothers you or that does not go away.

13. Appendix I, Sample Informed Consent, 'ARE THERE RISKS RELATED TO PREGNANCY'

The following changes have been made to this section:

Recently, some new information about DTG from another study being done in Botswana was reported. This study found that women taking DTG when they became pregnant appeared to be more likely to have babies with an abnormality called a neural tube defect than women who were taking other HIV medicines when they became pregnant. A neural tube defect is an abnormality of the spine or brain that can be severe. This abnormality can cause babies to die. Neural tube defects usually happen in about 1 out of every 1000 babies. In the Botswana study, neural tube defects were found in about 1 out of every 100 babies born to women who were taking DTG when they became pregnant. A baby's neural tube is formed in the first 4 weeks after conception. In the Botswana study, no neural tube defects were found in babies born to women who started taking DTG during pregnancy, after the neural tube had formed. The drug company and regulatory authorities and different researchers are looking into this issue to see if DTG really does cause neural tube defects. In the meantime, the U.S. FDA and other groups have recommended that women who are going to start taking DTG have a pregnancy test first. They also recommend that women use birth control to prevent pregnancy while taking DTG. HIV-infected women who are able to become pregnant are allowed to participate in this study, but they must use birth control (intrauterine device [IUD] or hormone-based contraceptive) in order to not become pregnant while in this study. If you do become pregnant while on study and taking the study drugs, you must call the study doctor right away.

The drugs used in this study may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant. Because of the risk involved, you must use at least one method of birth control. You must continue to use birth control for 6 weeks after stopping your medicines. You must choose one of the birth control methods listed below:

- ~~Condoms (male or female) with or without a spermicidal agent~~
- ~~Diaphragm or cervical cap with spermicide~~
- Intrauterine device (IUD) **or intrauterine system**
- Hormone-based contraceptive **(contraceptive subdermal implant, combined estrogen and progestogen oral contraceptive, injectable progestogen, contraceptive vaginal ring, and percutaneous contraceptive patches)**

If you do not want to use one of the birth control methods listed above, you will be taken off the study treatment, but asked to continue the study evaluations.

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. **Women who can become pregnant will have testing for pregnancy at every study visit.** If you think you may be pregnant at any time during the study, tell your study staff right away. **If you decide at any time while you are in this study that you want to become pregnant and start trying to become pregnant, you must tell your study staff right away.** If you are pregnant **or trying to become pregnant,** you will be taken off the study treatment, but asked to continue the study evaluations. The study staff will talk to you about your choices.

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in women taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

NOTE: It is not known whether the study drug passes through breast-milk and may cause harm to your baby. If you are breastfeeding, you cannot take part in this study.

14. 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