Letter of Amendment (version 2.0) to:

ATN 152

Triggered Escalating Real-time Adherence Intervention to Promote Rapid HIV Viral Suppression among Youth Living with HIV Failing Antiretroviral Therapy: The TERA Study

A Multi-Center Study Randomized, Controlled Trial of the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) Protocol Version 3.1 (20 January 2020)

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Letter of Amendment #1 (version 2.0) to:

ATN 152

Triggered Escalating Real-time Adherence Intervention to Promote Rapid HIV Viral Suppression among Youth Living with HIV Failing Antiretroviral Therapy: The TERA Study

A Multi-Center Study Randomized, Controlled Trial of the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN)Protocol

Version 3.1, dated 20 January 2020

Letter of Amendment 1 Version 2.0: 04 Septmeber 2020

Summary of Modifications and Rationale

1. Extension of week 48 visit window, as needed, due to COVID-19 study suspension

2. Change all secondary objectives to apply only to data collected prior to COVID-19 study suspension

3. Virtual/remote site monitoring

4. Virtual/remote week 48 study visit

Implementation

The information contained in this Letter of Amendment (LoA) impacts the ATN 152.

Modification 1. Extension of week 48 visit window, as needed, due to COVID-19 study suspension

On March 20th 2020 the study team implemented a full pause to all study procedures per TERA Memo #04-2020. At the time of implementation of the suspension of study activities, 36 participants were in follow-up on study. As sites re-open services, all of these participants will be reintegrated into their study timeline or asked to complete a final study visit if timeline has ended.

Section 7.7 Week-48 Visit (Off-Study Visit)

The Week-48 Visit is targeted to take place on Day 336, counted from the date of enrollment as Day 0, with an allowable window of ± 28 days, **or until end of data collection on September 28, 2020, if study visit window was during or after March 20, 2020**.

Modification 2. Change secondary objectives to apply only to data collected prior to COVID-19 study suspension

Due to the COVID-19 pause in data collection and potential dissimilarity between pre and post COVID-19 data points, the study team reviewed all planned analyses and adopted a new strategy. The new strategy considers study outcomes using two databases- a pre-COVID database representing all data collected prior to the COVID-19 study pause and an 'all available' database representing all data

available collected from the beginning to the end of the study (estimated closure of end of September 2020). All analyses identified in the protocol will be conducted first on the pre-COVID database and will focus on week-12 outcomes. Planned analyses for subsequent time points will include only participants with data available prior to the COVID-19 study pause. Given the anticipated reduction in sample size, outcome measures assessed after Week 12 will have reduced power to detect differences between arms. Data collected in post COVID visits will be combined with the pre-COVID database after study closure for additional targeted analyses.

Section 11.4.2 Secondary Outcome Measures

Secondary Objective #1. To estimate and compare virologic suppression rates in YLWH 24, 36, and 48 weeks after initiating TERA or continuing SOC

Outcomes:

- HIV-1 RNA < 50 copies/ml. **This analysis will only include participants with the opportunity to reach the targeted study visit prior to the COVID study pause.** Participants with HIV-1 RNA ≥ 50 copies/ml or **who had the opportunity to reach the study visit week and** with no HIV-1 RNA measurement within ± 28 days of the scheduled visit will be classified as failures.
- HIV-1 RNA < 200 copies/ml. **This analysis will only include participants with the opportunity to reach the targeted study visit prior to the COVID study pause.** Participants with HIV-1 RNA ≥ 200 copies/ml or **who had the opportunity to reach the study visit week and** with no HIV1 RNA measurement within ± 28 days of the scheduled visit will be classified as failures

Secondary Objective #2. To estimate and compare proportions of participants initiating TERA or continuing SOC who achieve virologic suppression (HIV-1 RNA < 200 copies/ml) by 12 weeks and maintain virologic suppression through 48 weeks

Outcome:

i. HIV-1 RNA < 200 copies/mL at weeks 12, 24, 36 and 48. **This analysis will only include participants with the opportunity to reach Week 48 prior to the COVID study pause.** Participants will be classified as virologic successes if both the Week-12 (± 14 days) and 48 (± 28 days) HIV-1 RNA measurements are < 200 copies/mL and at least one of the Week-24 (± 28 days) or Week-36 (± 28 days) HIV-1 RNA measurements is < 200 copies/mL. **Participants will be classified as failures if (1) either of the Week 12 or 48 HIV-1 RNA measurements are ≥ 200 copies/mL, (2) HIV-1 RNA at both Week 24 (± 28 days) and Week 36 (± 28 days) are ≥ 200 copies/mL, (3) both the HIV-1 RNA measurements between Weeks 12 and 48 are missing, or (4) either or both the Week 12 and Week 48 HIV-1 RNA are missing.**

Secondary Objective #3. To summarize and compare adherence patterns in YLWH initiating TERA or continuing SOC during the intervention period (weeks 0-12) and the post intervention period (weeks 12-48).

Outcomes:

- Electronic dose monitored adherence: Percent of days with all doses taken per week.

- Electronic dose monitored on-time adherence: Percent of days with all doses taken within the defined acceptable windows (±4 hours) per week.
- Electronic dose monitored non-persistence: Number of gaps (at least 7 consecutive days (168 hours) between doses) in the intervals: week 0-12, 12-24, 24-36 and 36-48.

Modification 3. Virtual/remote site monitoring
Due to COVID-19 travel restrictions and institutional policies, site monitoring visits planned on or after March 20, 2020 will be conducted using virtual/remote methods.

Section 8.8: Study Site Monitoring and Record Availability
Site monitors from the ATN coordinating center will visit participating study sites to review a selected portion of the individual participant records, including assent/consent forms, CRFs and supporting source documentation to ensure the protection of study participants, compliance with the protocol, and accuracy and completeness of records. Regulatory files, as required, will also be inspected to ensure that regulatory requirements are being followed.

The site investigator will make study documents (e.g., consent forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the NICHD, the Office of Human Research Protection (OHRP), or the sponsor's designee for confirmation of the study data.

Virtual/remote site monitoring may take place in lieu of an on-site visit. In these instances, site investigators must arrange for source documentation to be available either remotely or as certified copies. The ATN Coordinating Center will verify any virtual/remote methods used will comply with data security requirements as approved by the UNC Information Technology Services.

Modification 4. Virtual/remote Week 48 study visit
Due to restrictions by participating institutions regarding onsite research study visits during COVID-19 pandemic and/or research participants' preference for remote study visit due to COVID-19 concerns, the Week 48 study visit including eCRF and ACASI data collection may be conducted virtual/remotely.

7.7 Week-48 Visit (Off-Study Visit)
The Week-48 Visit is targeted to take place on Day 336, counted from the date of enrollment as Day 0, with an allowable window of ± 28 days. At this visit, participants will be informed of how to contact study staff with any post-study questions and how to learn about the results of the study when available. **This final study visit may be conducted virtually/remotely via a HIPAA compliant platform, such as VSee, per institution human subjects research policies or participant preference due to COVID-related circumstances.**

8.2.3.4 Participant Confidentiality
To ensure an even greater level of security and confidentiality, participants/study staff are required to enter a Personal Identification Number (PID) to gain access to the data entry forms. It is ONLY the PID that is stored with the collected survey data, thus ensuring that under no means may the collected survey data reveal a participant's identity. Participants will also complete the ACASI survey in a private clinic room further ensuring their answers remain confidential. **For Week 48 study visits that are**

conducted virtually/remotely via a HIPAA-compliant platform, site staff will confirm that the participant is at a private location and send the website link to the ACASI via a secure method, such as the chat function in VSee, to the participant to complete.