ATN 152: TERA

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

(Version 3.0, LOA#1)

Primary Statistical Analysis Plan

Version 3

ClinicalTrials.gov Identifier: NCT03292432

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This is ATN 152 SAP Version 3.0 with names of authors, names of publication writing team members and analysis timeline redacted.

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1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes analyses of the primary and secondary objectives of the TERA study. The Primary SAP outlines the general statistical approaches that will be used in the analysis of the study. It has been developed to facilitate discussion of the statistical analysis components among the study team, and to provide agreement between the study team and statisticians regarding the statistical analyses presented in the primary statistical analysis report. This analysis plan may be modified by the study team as new information becomes available outside of the study or to reflect recommendations of the SMC. In addition, some analyses may be omitted if there is insufficient information. Outlines of analyses for the other objectives will be presented in separate SAPs. Detailed outlines of tables, figures, and coding descriptions are included in a separate Analysis Implementation Plan (AIP).

The primary statistical report will be used for submission of results to ClinicalTrials.gov. Results for primary measures must be submitted within one year of the primary completion date (PCD), which for TERA is based on 12 weeks of follow-up. Results for secondary outcomes measures are due one year after follow-up is complete on all study participants.

1.2 Key Updates

Version	Changes Made	Rationale	Effective Date
1.0	Original Version		Dec 20, 2017
2.0	• Updated study population • Removed BID regimens	• Responding to Protocol Version 2.0 and SMC suggestions from June 2018 review • No changes needed for Protocol Version 3.0	April 4, 2019
3.0	• Changes to analysis due to COVID outbreak • Updates to secondary outcome measures • Clarification of how deaths are handled in virologic outcome measures	• Responding to changes in follow-up due to COVID outbreak	June 24, 2020

2 Protocol Overview

2.1 Study Design

TERA is a Phase II, randomized, open-label study designed to assess the effectiveness of a Triggered Escalating Real-Time Adherence (TERA) intervention for 12 weeks in Youth Living With HIV (YLWH) failing antiretroviral therapy (ART). This time-limited approach includes education and motivational skills building from an adherence coach and monitoring with wireless electronic dose monitoring (EDM), for identification of delayed and missed doses of antiretrovirals and related alerts and coach phone-based outreach.

The original design was to enroll 120 YLWH, stratify by age (<18 years vs. ≥18 years), and randomize with equal probability to TERA or continuing standard-of-care (SOC) for adherence. At entry, half were randomly selected to engage in additional in-depth interviews about their experiences at Weeks 12 and 48, with the goal of having 40 evaluable participants at both time points. Participants were followed for 48 weeks.

In August 2019, the Adolescent Trials Network Safety Monitoring Committee (SMC) recommended that accrual be closed and the 89 enrolled participants continue follow-up to study completion.

In March 2020, study visits were paused due to the outbreak of COVID-19. The study team decided to use the 'pre-COVID' database to analyze the primary and secondary objectives, since data collected after study visits resumed would be inherently different. This required a change to the definition of the virologic secondary outcome measures. It also meant that sample sizes at later study visits would be lower than anticipated, with a corresponding reduction in power to detect differences between arms. Additional data may be collected at study visits that take place after sites re-open. Analysis of these data will be outlined in a separate SAP.

2.2 Hypotheses

1. Youth in the TERA arm will be more likely to achieve viral suppression at Weeks 12 (primary), 24, 36 and 48 compared to youth in the SOC arm
2. Youth in the TERA arm will be more likely to achieve and sustain viral suppression than those in the SOC arm
3. Youth in the TERA arm will have higher rates of weekly dosing as measured by EDM over 48 weeks than those in the SOC arm
4. Viral suppression and adherence will be associated with gains in adherence-related information, motivation and behavioral skills, which will be higher in youth in the TERA arm than those in the SOC arm
5. Youth will report positive attitudes and experiences with the intervention on interview with themes emerging relative to adherence support that are unique from those in the SOC arm.

2.3 Objectives

Primary Objective:

1. To estimate and compare HIV virologic suppression rates in YLWH 12 weeks after initiating TERA or continuing SOC.

Secondary objectives:

1. To estimate and compare virologic suppression rates in YLWH 24, 36, and 48 weeks after initiating TERA or continuing SOC
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
3. To summarize and compare adherence patterns in YLWH initiating TERA or continuing SOC during on-intervention period (week 0-12) and post intervention period (week >12-48).

3 Definitions

"Study entry" is defined as the randomization date. The value used for baseline summaries will be the last evaluation on or before the randomization date.

Any youth found to be ineligible or who the Core Team determine should not be included in any analyses, will be included in screening, accrual and eligibility summaries only. Otherwise, analyses will be intent-to-treat (ITT), including all eligible participants randomized to the study and by randomized arm, regardless of compliance to the TERA intervention, SOC, or ART regimen.

4 Statistical Methods

4.1 General considerations

Baseline characteristics will be summarized by arm, but with no statistical comparisons. In general, categorical data will be summarized using N (%) and continuous data using N, key quantiles, and mean (STD) when appropriate.

Because of the interruption in study visits due to the COVID-19 pandemic in March 2020, analyses of the primary and secondary objectives will use the 'pre-COVID' study database including all data collected before study visits were paused. By March 2020, all participants had had the opportunity to reach Week 12, so analyses of the primary outcome measures were unaffected. However not all participants had had the opportunity to reach the Week 24, 36 and 48 timepoints. Only participants with the opportunity to reach each timepoint prior to the COVID-19 study pause will be included in assessments of the secondary outcome measures.

As this is a Phase II study, there are no *a-priori* statistical stopping guidelines. Statistical tests (all two-sided) will not be adjusted for interim monitoring, multiple comparisons or stratification for age. Significance levels $p<0.05$ will be highlighted in the text, but must be interpreted with caution since there will be many tests. Any changes to outcome measures after the analysis has begun will be identified as *post hoc*.

This Phase II clinical trial is not subject to NIH requirements that primary analyses of intervention comparisons be summarized by sex and race.

4.2 Visit schedule and analysis windows

Clinic visits take place at screening, entry (which may be the same day as screening), and Weeks 4, 12, 24, 36, and 48. All measures on or before the randomization date are grouped as Week 0,

with the value closest to and on or before the randomization date used as the baseline measurement. Scheduled visit windows for the week 4 and 12 visit is ± 14 days and for weeks 24, 36 and 48 the window is ± 28 days. Analysis visit windows will be formed around each study visit using the midpoints between adjacent weeks as cutoffs. If there are multiple evaluations within the window for a given visit, the evaluation closest to the scheduled study week will be used.

4.3 Outcome measure definitions

Primary objective: To estimate and compare HIV virologic suppression rates in YLWH 12 weeks after initiating TERA or continuing SOC.

This analysis will exclude participants dying before Week 12 for reasons unrelated to HIV.

Outcome measures:

i. HIV-1 RNA <50 copies/ml. Participants with HIV-1 RNA ≥ 50 copies/ml or with no HIV-1 RNA measurement within the Week 12 window (± 14 days) will be classified as failures

ii. HIV-1 RNA < 200 copies/ml. Participants with HIV-1 RNA ≥ 200 copies/ml or with no HIV-1 RNA measurement within the Week 12 window (± 14 days) will be classified as failures

Secondary objectives:

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

   These analyses will exclude participants dying before Week 24 (36, 48) for reasons unrelated to HIV.

   Outcome measures:

   i. 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

   ii. 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 HIV-1 RNA measurement within ± 28 days of the scheduled visit, will be classified as failures

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.

   This analysis will exclude participants dying before Week 48 for reasons unrelated to HIV.

   Outcome measure:

   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 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) and 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.

3. To summarize and compare adherence patterns in YLWH initiating TERA or continuing SOC during on-intervention period (week 0-12) and post intervention period (week >12-48).

   Outcome measures:

   i. Electronic dose monitored adherence: Percent of days with dose taken per week

   ii. Electronic dose monitored on-time adherence: Percent of days with dose taken within the defined acceptable windows (± 4 hours) per week.

   iii. 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.

5 Primary outcome measure analysis: short term virologic success at Week 12

The primary objective of the study is to estimate and compare HIV virologic suppression rates (HIV-1 RNA < 50 copies/ml and <200 copies/ml) 12 weeks after initiating the TERA intervention or continuing SOC. If more than one HIV-1 RNA measurement occurs within the allowable 28-day window, the highest value will be chosen. Other than participants dying for reasons unrelated to HIV before Week 12, all eligible participants will be included in this analysis, classifying those lost-to-follow-up as failures, Sensitivity analyses will repeat the primary analysis (i) using observed HIV-1 RNA only (participants with missing week 12 HIV-1 RNA not included in denominator), (ii) using a wider window around the Week 12 study visit, and (iii) using last observed HIV-1 RNA if missing week 12.

Virologic success rates in each arm and the difference in success rates between arms will be summarized with 95% confidence intervals (CIs). Analyses adjusting for covariates identified *a priori* by the study team will be conducted to assess whether the magnitude and strength of the association between the intervention and virologic success changes after adjustment for other factors.

6 Secondary outcome measures analysis

6.1 Longer-term virologic success at Weeks 24, 36 and 48

This outcome measure addresses virologic success rates after completion of the TERA intervention at Week 12, to assess the duration of its effect. The analytic approach will be similar to the primary outcome measure outlined in Section 5, conducting comparisons by arm at Weeks 24, 36 and 48, but with wider allowable windows (±28 days) around each study visit, and excluding participants who die for reasons unrelated to HIV before each timepoint. If more than one HIV-1 RNA measurement occurs within the allowable 56-day window, the highest value will be chosen. Sensitivity analyses will repeat the primary analysis (i) using observed HIV-1 RNA only (participants with missing week HIV-1 RNA not included in denominator), (ii) using a wider window around the study visit, and (iii) using last observed HIV-1 RNA. An analysis combining data from Weeks 24, 36 and 48 will use generalized linear models to account for the repeated measures for each participant.

6.2 Achieving and maintaining virologic success over 48 weeks

This outcome measure is achieving virologic success (HIV-1 RNA < 200 copies/ml) at Week 12 (±14 days) and maintaining virologic suppression through Weeks 24, 36 and 48 (all ±28 days). Success rates will be summarized and compared using the same approach as for the primary outcome measure, and excluding participants who die for reasons unrelated to HIV before Week 48.

6.3 Adherence

The Electronic Dose Monitoring (EDM) Device will capture whether participants opened the device (and presumably took their designated antiretroviral) and if it was within the allowable window (±4 hours) each day while on study. It is not possible to identify when doses were missed due to EDM functionality, lost or stolen devices, or lack of access to the EDM device due to hospitalization or incarceration. This means that adherence may be under-estimated in each arm. However since these situations should arise equally in the two arms, comparisons between arms should be unbiased.

6.3.1 Percent of days with doses taken per week

For each 24-hour window (defined as midnight to midnight), a participant will be classified as having taken their dose if they opened the EDM device, regardless of when in the 24-hour period. For each week (defined as day of study entry (e.g. Monday) plus 6 days (e.g. Sunday)), the percent of days with a dose taken out of days with data in that week will be calculated. These percentages will be summarized across participants in each arm by week and illustrated using a Figure. To address the issue of possible informative censoring of participants lost-to-follow-up for reasons other than death, a second summary will use available data while the participant is on study, and impute 0% for each week after a participant has been lost-to-follow-up and up to the earlier of March 20, 2020 or the date of what would have been their Week 48 study visit. The denominator for the second set of analyses will be the number of participants randomized to each intervention arm with the opportunity of follow-up to each week.

The number of days with a dose taken will be summarized during the intervention phase of the study using interval-censored methods. Participants lost-to-follow-up before 12 weeks will be assigned an interval between the number of doses recorded as taken (minimum possible assuming no further doses taken through full 12 weeks of follow-up) and that number plus the difference between 84 days (12 weeks) and the day they were lost-to-follow-up (maximum possible assuming all further doses taken through full 12 weeks of follow-up). Arms will be compared using a generalized logrank test. Note that this approach is different from the one outlined in the protocol which proposed using repeated measures rank sum tests to compare adherence between arms, as this approach relied on having complete data. A similar approach will be used to summarize adherence in the post-intervention phase (weeks >12 – 48), with the caveat that participants lost-to-follow-up before Week 12 will not be included in post-intervention summaries.

6.3.2 Percent of days with doses taken within defined acceptable windows per week

For each 24-hour window (defined as midnight to midnight), a participant will be classified as having taken their doses on time if they opened the EDM device within the allowable ±4 hour window. This outcome will be analyzed in the same way as the outcome in Section 6.3.1. Ability

to determine if the dose was taken 'on time' will depend on the target dose times being correct and updated in real time in the EDM device.

6.3.3 Electronic dose monitored non-persistence

The outcome measure will be calculated during each 12-week interval (0-12, >12-24, >24-36, >36-48) as the number of 7-day gaps between doses relative to the number of weeks with EDM data reported times 12. This represents an incidence rate (IR) for numbers of gaps of 7 days per 12 weeks on study. For example, each consecutive gap of 7 days will increase the participant's count by one, i.e. missing 20 consecutive days would count as two gaps and missing 22 days would count as three gaps.

Both the number of distinct gaps (regardless of length) and the length of each gap are of interest. The number of participants with at least one gap, the number of gaps regardless of length, and the maximum gap length will be summarized. Incidence rates will be summarized for each 12-week interval and compared within and across the four 12-week intervals by arm using generalized estimating equations with a Poisson link. This analysis does not take into account participants lost-to-follow-up and results will need to be interpreted with caution.

7 Report Components

Detailed descriptions of the content of each of the following sections are given in the AIP.

1. Study entry
    a. Screening
    b. Accrual
    c. Eligibility and stratification errors
2. Baseline characteristics
    a. Demographics
    b. Sexual identity
    c. Sex behavior
    d. Substance use
    e. Life events
    f. HIV cascade
    g. Health status
    h. Mental functioning
    i. HIV stigma
    j. Adherence
    k. Antiretroviral medication history
    l. Psychotropic medications
3. Study and intervention status
4. Data completeness and study implementation
5. Adverse Events and Serious adverse events
6. Changes in antiretrovirals
7. Changes in CD4 counts and %
8. Adherence support during trial participation (participant-level)
9. Primary outcome measures
10. Secondary outcome measures