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

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ABSTRACT

Background: Youth living with HIV (YLWH) are confronted with a number of self-care challenges that can be experienced as overwhelming in the context of the normal developmental processes that characterize adolescence and young adulthood. Challenges to antiretroviral therapy (ART) adherence create a sizable minority of YLWH with unsuppressed viral load in the United States (US). Interventions to promote sustained viral suppression in YLWH are needed.

Objective: To evaluate the efficacy of a tailored, remote coaching intervention utilizing electronic dose monitoring for unsuppressed YLWH.

Methods: The Triggered Escalating Real-Time Adherence (TERA) support project is a phase 2, multi-site clinical trial of an intensive 12-week remote coaching intervention conducted with 120 viremic youth (randomized 1:1 to intervention or standard of care) receiving care at a participating clinical care site within the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). All participants are followed for a total of 48 weeks, divided for those in the intervention condition into active intervention (first 12-weeks) and observation (remaining 36-weeks). Clinical outcomes are collected throughout the project, and adherence is assessed using Electronic Dose Monitoring (EDM) for all participants over the full 48-weeks. During the 12-week intervention period, intervention arm participants will receive: 3 remote coaching sessions delivered in-clinic via video-counseling and theory-informed coaching outreach through short message service (SMS) text messages or phone tailored to dosing and non-dosing as indicated by the EDM device. The primary outcome is viral suppression at 12-weeks, with secondary outcomes focused on more distal time points and more liberal cut-off for suppression. Other outcomes include patterns of adherence, psychosocial factors and extracted themes from interviews with participants, as well as costing data for implementation.

Results: Enrollment is expected to be completed by April 2019 and results presented by last quarter of 2020.

Conclusions: Effective, generalizable, scalable approaches to rapidly assist YLWH failing treatment to reach viral suppression can have a substantial impact on individual health and efforts to curb transmission. Coaching for a brief but intensive period from remote counselors trained and experienced in working with youth using communication channels common to youth may offer multiple unique advantages in promoting self-care.

Trial Registration: NCT03292432 Clinicaltrials.gov

Key words: HIV, adolescents, medication adherence, telemedicine
INTRODUCTION
Among the 35 million people living with human immunodeficiency virus (HIV) worldwide, 7 million are below the age of 24. With the concerted efforts to increase viral suppression globally and through strategic national plans, the unique sequela of youth living with HIV (YLWH) must be addressed to reach viral suppression goals. Successful progression through the continuum of HIV care is poorer among adolescents than adults in the US, with as many as 43% failing to reach and sustain HIV virologic suppression (VLS).[1] Even those accessing ART have elevated risks for failure to achieve VLS, with recent reviews suggesting that the subset of youth who achieve VLS after 48 weeks of ART is alarmingly low (27% to 89%).[2] Given that youth presently must remain on ART for the rest of their lives, sustaining suppression and limiting the exhaustion of available therapies is particularly critical. Importantly, because those failing ART are at increased risk of subsequent ART failure,[3, 4] interventions to improve adherence and disrupt patterns of non-adherence are critically needed for YLWH who fail to suppress virus on ART.

Despite elevated risk for repeated failure, a dearth of evidence exists on the issues, approaches, and facilitators/barriers for youth failing to achieve or sustain VLS, and recent reviews provide limited evidence for effective interventions for adherence support.[5, 6] Literature specific to adults failing first-line ART suggests that sex (female) and delayed start of second-line therapy predict lack of suppression by 24-weeks.[7] The evidence base in characterizing first-line ART failures and second-line outcomes in resource-limited settings is growing,[8] however, such correlates may not generalize to YLWH in the US. Moreover, the current focus on demographic factors provides limited guidance for intervention development. Thus, despite nearly two-decades of available effective ART, drivers of adherence for YLWH and how best to intervene to optimize adherence remain poorly understood.

YLWH are a unique cohort. Developmental tasks during this period of life create both the challenges and resources[9] that impact daily living for YLWH between the ages of 13 and 24. Youth would likely benefit most from strategies that specifically bridge the gaps common during adolescence caused by normal neuro-cognitive and emotional development.[10] Challenges in executive functioning and cognitive abilities are common among infected youth, even prior to ART initiation.[11] Further, social support, impulsivity constraining prospective planning, lability, increased needs for autonomy, and identity development need careful attention in programs focused on support YLWH. In this context, support for YLWH struggling with adherence that extends beyond and in-between clinical care visits through technology-based modalities may offer unique advantages, such as offering as-needed intervention in response to actual events through communication channels most commonly used by youth in the US. Specifically, real-time electronic dose monitoring to signal potential intervention opportunities, texting to explore needs and context surrounding such events, and phone delivered outreach to offer patient-centered coaching from a remotely located youth coach may be particularly well suited to the assets and needs of YLWH in the US.
Components of a Youth Focused Adherence Intervention
Promising components of a youth focused intervention were identified from existing evidence and theoretical models were considered for adaptation and inclusion. These include dose event monitoring, outreach between clinic visits (SMS texting and phone-based), remote coaching, and use of a time-limited though intensive program.

Dose Event Monitoring
Evidence supports the use of technology enhanced interventions to promote medication adherence among those living with HIV.[12] Recent work with adults in Cape Town, South Africa, evaluated an intervention approach that used SMS text messages to signal late doses according to a Wisepill™ device for first-line therapy ART.[13] A slight reduction in treatment interruptions was reported, although overall adherence, retention in care, and viral suppression did not appear improved for this cohort. Two-way, or interactive, SMS texting yoked to known delays in dosing, however, has not been rigorously evaluated with YLWH in a randomized, controlled trial.

Outreach between clinic visits
Text. SMS text-based strategies [14] [15], that are not yoked to monitoring but are systematically sent, require a response from participants, and also seem to suggest that an interactive component is particularly beneficial.[16] [17] Garofalo and colleagues recent work in this area with 105 adolescents and young adults where two-way daily SMS texts were provided to non-adherent youth demonstrated a significant improvement in self-reported adherence and high satisfaction scores.[18] Furthermore, a pilot study using personalized, interactive, daily SMS text messages demonstrated significant improvement among 14-to-29 year olds living with HIV with poor self-reported adherence rates.[19]

Phone Based Outreach.
Evidence has supported the utility of phone-based outreach using a problem solving approach.[20] [21] In a recent review, harnessing mobile phone technology was identified as a promising area for future interventions encouraging optimal adherence among YLWH.[18] Furthermore, evidence suggests using phone-based technology to engage adolescent social support networks may promote optimal engagement in care and adherence to medications. [22, 23] A recent study of a phone-based support intervention among non-adherent YLWH found that it was acceptable and feasible among youth and clinic staff.[24]

Coaching at clinic visit.
Coaching has been defined as a patient-centered strength-based approach that tends to be time-limited, focused on problem solving and health and wellness, and goal oriented, which differs from counseling predominantly in explicit focus on current lifestyle and more narrow scope and depth.[25] Coaches tend to provide when and as needed support and check-ins [25] and the approach has gained support in addressing diverse health behaviors, including weight management, exercise, and overall physical health[26]. In a review of coaching interventions, approaches that included goal setting and motivational interviewing...
demonstrated stronger outcomes [27]. Despite promise for marginalized groups[28] and for adolescents[29], coaching work has largely focused on adults to date.

**Time-limited**
Adolescent focused 'brief interventions' have received considerable attention as well-matched to development tasks in youth [30] and demonstrating positive effects on alcohol and drug use [31]. Moreover, in consideration of intervention approaches that involve monitoring and outreach, positioning the program as “intense but time-limited” may arguably allow for better engagement.

**Overview of the TERA Project Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) Protocol 152**
To support YLWH failing ART due to non-adherence, the TERA project (ATN 152) will evaluate a novel, evidence-informed, triggered, escalating, real-time adherence intervention that leverages contemporary technology to address a key area of need as it relates to the continuum of care among YLWH. TERA is a time-limited (12 weeks) intervention approach that (a) uses wireless EDM to identify dose-times passing with no bottle opening, (b) sends an SMS text asking about the delay, (c) evaluates response to SMS text and (d) initiates follow-up by an adherence coach depending on response and if the bottle remains unopened for a designated period post dosing time. Phone based outreach uses patient-centered coaching, informed by problem solving [32], Motivational Interviewing (MI) [33], Next Step Counseling (NSC) [34, 35], Positive Youth Development theory [9] and the Information Motivation Behavioral Skills (IMB) model situated to YLWH (sIMB [36]). The TERA intervention will be compared with a standard of care (SOC) control condition on VLS at 12, 24, 36, and 48 weeks, EDM rates of ART adherence at the same time points and patterns of adherence over time, among 120 YLWH across multiple participating sites in all regions of the US in the Adolescent Medicine Trials Network for HIV/AIDS Interventions. The study objectives and hypotheses are listed in Table 1.

**TABLE 1. Objectives, Outcomes, Hypotheses**

<table>
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<tr>
<th>Level</th>
<th>Objective</th>
<th>Measure(s)</th>
<th>Hypothesis</th>
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| Primary     | To estimate and compare HIV virologic suppression rates in YLWH 12 weeks after initiating TERA or continuing SOC. | **HIV-1 RNA <50 copies/ml.**  
              |                                                                           | **HIV-1 RNA < 200 copies/ml.**                                                           | Youth in the TERA arm will be more likely to achieve viral suppression (VLS) at week 12 compared to youth in the SOC arm<sup>a</sup> |
| Secondary   | To estimate and compare virologic suppression rates in YLWH 24, 36, and 48 weeks after initiating | **HIV-1 RNA < 50 copies/ml.**  
<pre><code>          |                                                                           | **HIV-1 RNA &lt; 200 copies/ml.**                                                           | Youth in the TERA arm will be more likely to achieve VLS at weeks 24, 36 and 48 compared to youth in the SOC arm&lt;sup&gt;b&lt;/sup&gt; |
</code></pre>
<p>| Objective #1|                                                                           |                                                                            |                                                                                              |</p>
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<tr>
<td>Secondary</td>
<td>To estimate and compare proportions of participants initiating TERA or continuing SOC who achieve virologic suppression (HIV-1 RNA &lt; 200 copies/ml) by 12 weeks and maintain virologic suppression through 48 weeks</td>
<td><em>HIV-1 RNA &lt; 200 copies/mL at weeks 12, 24, 36 and 48</em></td>
<td>Youth in the TERA arm will be more likely to achieve and sustain VLS than those in SOC arm</td>
</tr>
<tr>
<td>Secondary</td>
<td>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).</td>
<td><em>Electronic dose monitored adherence</em> (percent of days with all doses taken per week), on-time adherence (±4 hours for QD and ± 2 hours for each dose if BID), and non-persistence (number of gaps [at least 7 consecutive days (168 hours) between doses]) between week 0-12, 12-24, 24-36 and 36-48)</td>
<td>Youth in the TERA arm will have higher rates of weekly dosing as measured by EDM over 48 weeks than those in SOC arm</td>
</tr>
<tr>
<td>Other</td>
<td>To evaluate and compare changes in survey collected social-psychological factors by study arm, and establish the extent to which these changes are associated with adherence and viral load outcomes.</td>
<td>Change in ACASI collected scales for information, motivation and behavioral skills, as well as emotion regulation and functioning and decision making</td>
<td>VLS 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</td>
</tr>
<tr>
<td>Other</td>
<td>To identify profiles (phenotypes) of EDM measures listed in Secondary Objectives #3</td>
<td>NA</td>
<td>NA</td>
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**Note:** EDM = Electronic Dose Monitoring, VLS = Virologic Suppression, TERA = Team-Based Educational and Relational Approach, SOC = Standard of Care.
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<th>Level</th>
<th>Objective</th>
<th>Measure(s)</th>
<th>Hypothesis</th>
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<tbody>
<tr>
<td>#2.</td>
<td>adherence based on EDM data</td>
<td></td>
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<tr>
<td>Other Objective #3</td>
<td>To describe the resource requirements and costs of the TERA intervention, including the AdhereTech™ bottles, virtual coaching software, SMS messages, and personnel time and salaries.</td>
<td>Cost for implementation of the intervention transformed into a per participant fixed and variable cost estimates</td>
<td>NA</td>
</tr>
<tr>
<td>Other Objective #4</td>
<td>To characterize through qualitative interviews, the main themes youth report for adherence support needed, received, and valued at 12 and 48 weeks.</td>
<td>Thematic content of interview inquiries.</td>
<td>NA</td>
</tr>
<tr>
<td>Other Objective #5</td>
<td>To evaluate acceptability and feasibility of participation in the intervention with mixed methods (interviews and ACASI survey).</td>
<td>Satisfaction Survey at week-12 ACASI for all TERA arm participants, semi-structured interview data</td>
<td>Youth will report positive attitudes and experiences with the intervention content with themes emerging relative to adherence support that are unique from those in the control arm</td>
</tr>
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</table>

*Participants with no HIV-1 RNA measurement within the allocated Week-12 study visit window (± 14 days) will be classified as failures*

*Participants with no HIV-1 RNA measurement within the allocated study visit window for weeks 24, 36, or 48 (± 28 days) will be classified as failures*

*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*
The primary objective, 12-week viral suppression, will be measured at the week 12 visit when the final coaching session occurs, thus representing the effects at the intervention’s end. The secondary objective of longitudinal efficacy of the coaching sessions on viral suppression will be monitored over the following 36 weeks. The total time for participation will be 48 weeks - 12 weeks of intervention delivery and 36 weeks of follow-up.

**Theoretical basis for intervention.**
The TERA intervention uses EDM to signal coaching opportunities, while the implementation of coaching draws heavily from the IMB model situated within socio-ecological and positive youth development frameworks (Figure 1).
FIGURE 1: Theoretical Underpinning of TERA Intervention

Socio-ecological Levels for YLWH

- Sociocultural/Political
  - Systematic discrimination/stigma
  - Rights/laws
  - Political climate
  - Education/employment
- Social, political, cultural identities

- Institutional/Community services
- Public transportation
- Local groups
- Violence/safety
- Clinic characteristics
- Local school system
- Gangs, drugs, blight
- Stigmas
- Community identity

- Inter-personal/Social
  - Family, friends
  - Romantic relationships
  - Mentors/significant adults
- Connectedness
- Esteem/other-orientation
- Provider/staff relationship
- Stigmas
- Social network identities

- Intra-personal/Self
  - Knowledge
  - Internalized beliefs/values
  - Attitudes
  - Emotional regulation
  - Resiliency
  - Dreams/aspirations
  - Meaning of self-care
  - Self-valuation/internalized stigma
  - Mental health (trauma, depression, drug use)
  - Self-identity

sIMB Model

- Information
- Behavioral Skills
- Care Task
- Health Outcomes

Positive Youth Development

- Positive Youth Development Assets
  - External–Support, Empowerment, Boundaries/expectations, activities/programs
  - Internal–Learning/motivation, positive values, social competencies

- Select Positive Youth Development
  - Opportunities
  - Bonding
  - Resilience
  - Competencies (social, emotional, cognitive, behavioral, values)
  - Self-determination, efficacy
  - Clear and positive identities
  - Belief in future
  - Reinforcement for pro-health and pro-social behavior
  - Reinforcement for social engagement/involvement
The IMB model of ART adherence,[37] which has been used extensively in interventional adherence enhancement research [38, 39] and has a developed evidence base in diverse groups of adults [39] [40] [39, 41], is used as the basis for understanding specific adherence and non-adherence events. We use the situated-application of the model (sIMB)[36] to further embed the kinds of knowledge, personal and social consequences of adherence and non-adherence in the context of daily life, and skill sets needed for youth to navigate adherence in the context of self, others, and systems. Tailored understanding of each of the core IMB model constructs as expressed within and between the layers of the socio-ecological model (Figure 1 far left) is further refined with a Positive Youth Development lens (Figure 1 far right), which calls attention to the resources and opportunities unique to adolescents and young adults and critical in fostering positive awareness of, attitudes towards, and skills in promoting self-care. The coaching intervention uses this synthesized model to guide efforts to engage youth in their current context, within their particular landscape of resources and gaps. While the models in Figure 1 form the backbone of understanding for how adherence may be optimized or derailed, implementation of coaching discussions are guided by NSC, which draws on MI. NSC, MI and specifics for coaching in terms of theory and implementation are detailed in the intervention section. In summary, the aim of the TERA study is to evaluate a novel, evidence-informed triggered, escalating, real-time adherence intervention (TERA) that leverages coaching and contemporary technology to promote viral suppression among YLWH who have failed on ART.

METHODS
Trial Design Overview
TERA is a Phase II, randomized, open-label study evaluating the efficacy of the TERA coaching 12-week intervention in YLWH failing ART. On-hundred and twenty YLWH between the ages of 13 and 24 will be randomized with equal probability to the TERA intervention or continuing SOC, with stratification by age (<18 years vs. ≥ 18 years). At entry, 40 participants (20 from each arm) will be randomly selected to engage in additional in-depth interviews, at study weeks 12 and 48, about their experiences around adherence and self-care, as well as their experiences being in the study.

Study Setting
Clinical research sites within the ATN and the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) network in the US were solicited for interest in participation in ATN 152. A total of 9 clinical research sites are engaged in the trial, including sites in Alabama, California, Colorado, Florida, Maryland, Michigan, New York, and Tennessee. Clinical research sites differ in demography of clinic populations reflecting the specific characteristics of the HIV epidemic with youth in their region. Total anticipated targets for enrollment also vary between clinical research sites, ranging from 5 to 20 youth. All sites are experienced research sites that also operate as clinical care centers for youth. For the TERA project, a minimum of a site-level principal investigator and a study coordinator are required. Prior to initiation of the study
protocol at any site, activation activities are completed. The University of North Carolina at Chapel Hill (UNC-CH) serves as the single Institutional Review Board (sIRB) and has reviewed and approved the study for study sites.

Participants
A total of 120 participants will be enrolled. Eligible participants are YLWH, 13 to 24 years of age (inclusive), and in care at one of the participating sites. They must have failed first-line ART therapy, defined as having detectable HIV virus (HIV-1 ribonucleic acid (RNA) ≥200 copies/ml) within 45 days of enrollment despite having been on ART for at least 24 weeks. A complete list of eligibility criteria are included in Table 2.

Table 2. Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
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<tbody>
<tr>
<td>1 Age</td>
<td>13-24</td>
</tr>
<tr>
<td>2 Confirmed HIV positive status</td>
<td>Confirmation of HIV-1 Infection as documented in the participant’s medical record by at least two criteria</td>
</tr>
<tr>
<td>3 Aware of HIV status</td>
<td>Site staff determined</td>
</tr>
<tr>
<td>4 Viremic</td>
<td>Documented plasma HIV-1 RNA plasma ≥200 copies/mL Within 45 days of enrollment*</td>
</tr>
<tr>
<td>5 On ART</td>
<td>Prescribed antiretroviral therapy at least 24 weeks or more prior to documented plasma HIV-1 RNA plasma ≥200 copies/mL</td>
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<td></td>
<td>Prescribed a once-a-day (one or more pills once a day) ART regimen with at least two active agents (per clinician judgment or genotype evidence) at enrollment</td>
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<tr>
<td>6 Language</td>
<td>Able to communicate in spoken and written English</td>
</tr>
<tr>
<td>7 Technology Access</td>
<td>Currently has a cellular phone that is able to send and receive SMS text messages</td>
</tr>
<tr>
<td>8 Retention</td>
<td>Willing and able to provide at least one additional contact phone number (preferably two) to be able to contact participant</td>
</tr>
<tr>
<td>9 Consent/Assent</td>
<td>Able and willing to provide written informed assent/consent and able to obtain written parental or guardian permission to be screened for and to enroll in this study</td>
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<tr>
<th>EXCLUSION CRITERIA</th>
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<tbody>
<tr>
<td>1 Cognitive Capacity</td>
<td>Gross cognitive limitations, acute emotional instability, or medical or mental health illness that would impair the individual's ability to provide informed consent and/or interfere with the protocol's objectives.</td>
</tr>
<tr>
<td>2 Concurrent participation</td>
<td>Concurrent participation in interventional studies addressing adherence ** Unless approved in advance by study team</td>
</tr>
<tr>
<td>3 Pregnancy</td>
<td>Positive pregnancy test at the time of enrollment **If participant becomes pregnant while on study, they may continue on study</td>
</tr>
<tr>
<td>4 Current use of EDM</td>
<td>Currently using or planning to use an electronic dose monitoring and reminder device outside of the study</td>
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Sample Size/Power
The study was designed to have 85% power to detect a difference in virologic suppression rates at Week 12 between the TERA and SOC arms of 25% (assuming a success rate of 60% on SOC). Participants lost-to-follow-up before Week 12 will be classified as failures, so no adjustment was made for loss-to-follow-up in the sample size/power calculations.

Randomization
Participants will be randomized to the TERA or SOC study arms with equal probability. Randomization will be stratified by age only to ensure balance in treatment assignments, and institutional balancing will be used to help ensure roughly equal balance in intervention assignments within each site. Once randomized to study arm, 40 participants (20 in each arm) will be randomly selected to participate in in-depth interviews at weeks 12 and 48. If refusal rates for interview participation at Week-12 are higher than expected, probabilities of selection will be increased during accrual.

Participant Timeline
Participants are enrolled for 48 weeks of study participation. Those assigned to the intervention condition will receive the intervention during their first 12 weeks of participation, which is then followed with 36 weeks of observation for a total of 48 weeks. All participants are asked to attend study visits at weeks 4, 12, 24, 36 and 48. All participants are asked to dose from an EDM (AdhereTech’s™ smart bottle) for their full 48 weeks of study participation. The participant experience is depicted in Figure 2.

Compensation
Compensation will be provided for participants at each study visit. The amount of compensation will be determined by the local study site staff and will be confirmed with the sIRB and will be
reflected in the site-specific informed consent form. Recommended incentives include $75 per visit through week 12 (first 3 study visits), $40 per visit for weeks 24, 36, and 48 and added incentives for the final week 48 visit ($100) for a possible total of $445 over the full 48-weeks. Additionally, participants randomly selected for the qualitative interviews receive $50 per interview for a possible total of $100. Participants in the intervention are not provided incentives for engagement in intervention sessions or outreach.

Virtual Youth Advisory Boards (vYAB)
Each participating clinical research site is asked to identify and engage at least two YLWH (between the ages of 13 and 24) to participate in vYABs for the study. These advisory meetings are hosted at the clinic site and use the interactive remote coaching/counseling software program (VSee) with all site youth advisory boards (YABs). Topics discussed include impressions of main challenges for YLWH, vetting ideas about intervention components and study implementation factors, and ensuring that the study and intervention is remaining relevant to the issues germane to YLWH in the regions engaged in the study. vYAB members are reimbursed for their contributions as consultants per meeting attended. Suggested reimbursement is $50 per meeting and clinical research sites are provided with food/beverage resources for hosting these meetings. The vYAB meets a minimum of quarterly and as needed.

Study Conditions - Standard of care
SOC relative to adherence support will be recorded for each participant during their study participation. In previous work we have developed a SOC measure for ART adherence support [42] that follows international recommendations for strategies [43], as well as strategies known to have positive effects [44] in some populations. There are no restrictions on participant SOC adherence support during the study for participants; however, the use of another EDM is not allowed while enrolled.

Study Conditions - Intervention
Components of the intervention implemented over the 12-week intervention period include: (1) remote education/preparation through counseling and planning with the assigned adherence coach (on computer at clinic site at baseline and weeks 4 and 12, as needed and as-available in between visit coaching sessions); (2) one-way SMS text message alert at dose time when bottle has not yet been opened for that dosing window (users can disable this on request); (3) missed dose two-way interactive outreach SMS text message asking “What’s the plan?”; and (4) implementation of the coach-outreach (phone, SMS text message, remote counseling) triggered by missed doses or as a check-in. Intervention components are described below.

Face to Face Remote Coaching (Baseline, Week-4 and Week-12).
Youth assigned to the TERA intervention condition at baseline will meet with their assigned adherence coach in a private clinic location via web-enabled virtual counseling (VSee software program). These trained coaches are not part of the clinic team; rather they are centrally located at the University of Michigan. The first session is anticipated to last up to 60 minutes, and includes building rapport, discussing roles and expectations, explaining the intervention
components, exploring resources, values and aspirations, and detailing current adherence strategies, strengths, challenges, and building an adherence plan. Additional details about the EDM bottle, SMS text messaging, and between clinic visit contacts will be explained. Details for the contact tree, black-out times (times when the participant does not want to be contacted and when coaches are not available), preferred name and appropriate pronouns, and other important aspects of the participant’s life that need to be considered throughout the interactions with coaches will be documented through “notes” and entered by the coach in a profile area on a TERA implementation dashboard. Coaches meet again with youth in set intervals, at week-4 and week-12 clinic visits, but may also interact with youth between visits through EDM-triggered contact or youth requested contact, which may be conducted through SMS text messaging, phone call or VSee video enabled contact. The final intervention session (12-week) includes detailed discussion about local and in-clinic resources should the participant want to continue working on adherence or other related issues and also includes a certificate of completion. All in-clinic, remote counseling sessions are audio recorded, unless a participant specifically declines, and stored securely for use in coach supervision and potential coding to characterize implementation of intervention at a later date.

Coaches receive training on brief counseling techniques and intervention-specific skills and material prior to the study. Coaches complete two MI workshops and one NSC workshop, and participate in several simulated sessions to practice techniques and skills. MI [33] has a long history of use in brief interventions, with promising results on improving adherence for YLWH[45], and NSC [34, 35] has been adapted to ART adherence among youth for this project. Intervention material is contained in an intervention manual, with basic steps articulated for each planned face-to-face session, monitoring of tickets, appropriate and allowable response and outreach strategies, and documentation requirements are detailed.

Triggered Outreach. The sequential escalation of adherence support follows a set pattern, where late and no dosing prompts increased efforts to connect and work with youth. The EDM device used in TERA, AdhereTech’s™ smart bottle, follows an algorithm to determine whether opening the device “counts” as a dose depending on previous opening dates and times, number of doses per day, and scheduled dose time(s). Opening events are thus classified as linked to a given dose and further characterized as early, on-time or late. Events that are not connected to a dose time are also recorded, which allows for continuous tracking of all opening events throughout study participation. For doses that do not have an opening event within the specified window preceding the dose time or 1.5 hours after the dose time has passed, an alert is sent to the TERA Dashboard, where all intervention implementation data is tracked and stored. This alert starts a ‘ticket’ within the TERA Dashboard system that includes an immediate SMS text message to a participant’s cell phone asking “What’s the plan? Reply a) taking now, b) took already, c) taking later, d) other, e) pass”. Each ticket is managed in real time by the study team member who is monitoring the TERA Dashboard (the Monitor). Monitors have specific shifts where they oversee activities in the TERA Dashboard and determine when escalation to a participant’s assigned coach is needed. Monitors include study trained coaches and designated, trained study team members. Using monitors allows for coverage of the TERA Dashboard 7-days a week, 7am Eastern Standard Time (EST) to 9pm EST each day.
Participant replies to texts initiated by the dashboard are investigated by the monitor to determine the details of the event using information from the participant’s profile and previous interactions documented on the TERA dashboard. The “event” may result in escalation to the participant’s coach who then reaches out to the participant. Participants are aware of the use of a monitor and interactions with the monitor and participant are permissible to collect basic additional information. The monitor can determine that an alert is resolved through their monitoring of the EDM dashboard (e.g., an opening event is recorded after the participant was texted). When issues are beyond clarifications, the participant’s coach is notified and the coach reaches out to the participant as soon as possible, and, per intervention design, within 24-hours. Monitors also notify the participant if there is a situation that will delay contact from the coach and can offer to connect the participant with a back-up coach. All such events are documented in the TERA Dashboard. Additionally, when participants fail to respond to an SMS text message within an hour and the monitor does not see activity on the EDM dashboard, the event is escalated to the coach.

**Escalated outreach.** In response to escalated ‘tickets’, coaches follow the principles of patient-centered counseling and use MI and problem solving strategies to assist youth in exploring context and drivers of event, facilitating insights into resolution(s), and tailoring discourse to identify next steps. Case notes are used in the TERA Dashboard to document discussions and agreed upon next steps. All SMS text messages are tracked in the Dashboard’s texting feature. Other discourse (via phone or remote counseling VSee software) is documented through the case note. If a coach cannot contact a participant, the contact tree (see below) is used.

**Contact tree.** In the event that coaches cannot reach youth via any agreed upon modality (phone, SMS text message, social media), the participant’s contact tree will be used in the order in which the youth listed contacts. The coach will implement all agreed upon forms of outreach to contact the youth, with the final attempt being outreach to the clinical research sites for assistance in establishing contact.

**Additional outreach and coach contact.** For each 7-day period with no tickets (no late or non-dosing) participants receive a check-in text (‘Checking in. All good? Y yes, N no”). Whereas other SMS text messages triggered by EDM require a reply within 1 hour, a response to these check-in messages is expected within 24 hours. For any response indicating need to connect with coach (i.e., No), the monitor reaches out to the coach for follow-up and informs the participant of anticipated time to contact from coach (i.e., I reached out to [coach name] and they will get back to you in the next 30 minutes). For participants not responding to the check-in SMS text message within 24-hours, a follow-up repeat SMS text message is sent the following day and another 24-hour period is allotted for response. If non-response persists, the ‘ticket’ is escalated to the coach.

During the 12-week intervention period, participants may text their coach directly. This SMS text message is received through the TERA Dashboard and creates a ‘ticket’ that is managed by the
monitor and potentially escalated to the participant’s coach for outreach.

**Measures**
Data collected includes responses to Audio Computer Assisted Self Interviews (ACASI) scales and items, estimated adherence through collection of ‘opening events’ from the EDM, and chart extracted data. In addition, implementation data is collected to provide costing data. Finally, qualitative interviews are conducted to further explore feasibility, acceptability and overall experiences in the project.

ACASI data are collected at baseline, week-12, week-24, week-36, and week-48. Table 3 describes each measure used in the ACASI as well as the schedule for data collection and brief description of the measure. The ACASI should take approximately 30-minutes or less to complete.

**TABLE 3. LIST OF STUDY MEASURES AND COLLECTION TIME-POINTS**

<table>
<thead>
<tr>
<th>Measures</th>
<th>Collection Method</th>
<th>Time Point</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence Support During Participation</td>
<td>ACASI</td>
<td>Week-12, Week-48</td>
<td>Check list of receipt of specific kinds of support during first 12 weeks and at week-48</td>
</tr>
<tr>
<td>Information Motivation Behavior Skills ART Adherence Questionnaire[46, 47]</td>
<td>ACASI</td>
<td>Baseline, Week-12, Week-24, Week-36, Week-48</td>
<td>Measure of adherence barriers identified by the Information, Motivation, Behavioral Skills Model of Adherence.</td>
</tr>
<tr>
<td>The HIV Adherence Self-Efficacy Scale[48]</td>
<td>ACASI</td>
<td>Baseline, Week-12, Week-24, Week-36, Week-48</td>
<td>Measures self-efficacy for adherence to HIV treatment plans, including, but not limited to taking HIV medications. The overall self-efficacy scale score as well as integration and perseverance subscales will be used for study purposes.</td>
</tr>
<tr>
<td>Adolescent Decision Making Questionnaire (ADMQ)[49]</td>
<td>ACASI</td>
<td>Baseline, Week-12, Week-24, Week-36, Week-48</td>
<td>Revised version of the ADMQ that measures decision making patterns in adolescence. Four subscales will be used for this study: avoidance, self-confidence, panic, and impulsive/thoughtless</td>
</tr>
<tr>
<td>CESD-10[50]</td>
<td>ACASI</td>
<td>Baseline, Week-48</td>
<td>Self-reported 10 item screening instrument designed to measure symptoms of depressed mood in respondents. Higher scores indicate increased depressive symptomology.</td>
</tr>
<tr>
<td>Demographics</td>
<td>ACASI</td>
<td>Baseline</td>
<td>Study developed and ATN harmonized</td>
</tr>
<tr>
<td>Measures</td>
<td>Collection Method</td>
<td>Time Point</td>
<td>Description</td>
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<tr>
<td>Emotional Regulation Questionnaire (ERQ)</td>
<td>ACASI</td>
<td>Baseline, Week-12, Week-24, Week-36, Week-48</td>
<td>10-items scale designed to measure respondents' tendency to regulate their emotions in two ways: cognitive reappraisal and expressive suppressive. Higher scores indicate greater use of emotion regulation strategy.</td>
</tr>
<tr>
<td>EQ-5D-Y (Overall health status)[52]</td>
<td>ACASI</td>
<td>Baseline, Week-12, Week-24, Week-36, Week-48</td>
<td>Standardized measure of overall health status designed to provide a simple measure of health for clinical appraisal. Provides a descriptive score for 5 dimensions: mobility, looking after myself, doing usual activities, having pain/discomfort, and sad or happy. A visual analogue scale item records respondent's self-rated health on a vertical scale to quantitatively measure respondents' self-reported overall health status.</td>
</tr>
<tr>
<td>HIV Cascade Measure (U24)</td>
<td>ACASI</td>
<td>Baseline</td>
<td>ATN harmonized items related to engagement in HIV related care.</td>
</tr>
<tr>
<td>Life Events Survey (LES)</td>
<td>ACASI</td>
<td>Baseline, Week-12, Week-48</td>
<td>Study adapted measure of significant or traumatic life events</td>
</tr>
<tr>
<td>Satisfaction Scale (Developed for study)</td>
<td>ACASI</td>
<td>Week-12, Week-48</td>
<td>Study developed measure of participants' satisfaction with the TERA intervention.</td>
</tr>
<tr>
<td>Self-Reported Adherence[54]</td>
<td>ACASI</td>
<td>Baseline, Week-12, Week-24, Week-36, Week-48</td>
<td>3-item self-reported measure of adherence to HIV medications - <strong>Doses taken</strong> (0 to 30), <strong>frequency</strong> of doses taken in last 30 days (Likert response), and rating of how good of a job taking medications (Likert response).</td>
</tr>
<tr>
<td>Sex Behavior</td>
<td>ACASI</td>
<td>Baseline, Week-12, Week-48</td>
<td>Brief item set to assess rates of condomless sex</td>
</tr>
<tr>
<td>Social Support Scale (MOS)[55]</td>
<td>ACASI</td>
<td>Baseline, Week-12, Week-24, Week-36, Week-48</td>
<td>Measure designed to assess overall functional social support as well as four separate social support subscales: emotional/information support, tangible support, physical support, emotional support, and financial support.</td>
</tr>
<tr>
<td>Measures</td>
<td>Collection Method</td>
<td>Time Point</td>
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<td>Measures</td>
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<tr>
<td></td>
<td>ACASI</td>
<td>Baseline,</td>
<td>Screening measure designed for use in primary care settings to screen for problem or risky use of tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, opioids and “other drugs” that do not fall into the previous categories. Higher scores for each substance use category indicate greater risk of experiencing severe problems as a result of substance use as well as greater risk for substance dependence.</td>
</tr>
<tr>
<td></td>
<td>AdhereTech™ EDM Device</td>
<td>Continuously during study participation</td>
<td>Smart pill bottle that monitors bottle openings on a continual basis. Data will be used to assess medication adherence and persistence. Adherence data will only be available centrally for coaches and will not be available for site clinic/study staff.</td>
</tr>
<tr>
<td></td>
<td>Chart abstraction and/or participant interview</td>
<td>Baseline, Week-12, Week-12, Week-24, Week-36, Week-48</td>
<td>Study developed checklist completed by study staff to document standard of care adherence support services received by participant.</td>
</tr>
<tr>
<td></td>
<td>Chart abstraction</td>
<td>Continuously during study participation</td>
<td>HIV-VL and CD4 count/percentage will be abstracted from participants’ medical records. HIV-VL results are required at each study visit if not already available. All other HIV-VL and CD4 results collected for routine care during study participation will also collected.</td>
</tr>
<tr>
<td></td>
<td>Chart abstraction</td>
<td>Baseline, Week-12, Week-24, Week-36, Week-48</td>
<td>Date of HIV diagnosis, route of HIV transmission, previous HIV antiviral medication exposure, AIDS defining illnesses and OIs since diagnosis, as well as current co-morbidities and concomitant medications will be abstracted from participants’ medical record.</td>
</tr>
<tr>
<td></td>
<td>Virtual Interview</td>
<td>Week-12, Week-48</td>
<td>To characterize the main themes youth report for adherence support needed, received, and valued, qualitative</td>
</tr>
</tbody>
</table>
Statistical Methods
The primary and secondary objectives of this study are to estimate and compare virologic suppression rates and adherence over 48 weeks between the TERA and SOC arms. Analyses will be intent-to-treat (ITT) using all participants as-randomized. Participants lost-to-follow-up before key time points or with no HIV-1 RNA measurement within allowable windows will be classified as failures at that time point. Categorical outcomes will be summarized using proportions (95% confidence intervals) and continuous outcomes will be summarized using means/medians as appropriate. In adjusted analyses, the number of covariates used in the models will be limited because of the relatively small sample size. Potential factors of interest in terms of influence on intervention effect include age, route of HIV infection, years living with HIV, regimen line (e.g., first, second) and substance use. A significance level of $P < 0.05$ will be used with no adjustments for multiple comparisons or interim analyses.

The EDM will provide daily information on adherence in each participant. Two outcomes (percent of days correctly dosed per week and percent of days dosed within the targeted time frame per week) will be summarized by arm by week, in 12-week intervals, and during and post-intervention. Differences may be largest during the initial 12 weeks, since that is when the intervention is administered, with differences waning over time. To address possible informative censoring induced by losses-to-follow-up, analyses will include (i) available data and (ii) imputing weekly adherence of 0% after a participant has been lost-to-follow-up.

To characterize TERA implementation, ability to enroll to the study, drop-out rates by Week-12 and throughout the study, numbers of participants escalating to different alerts and outreach at least once, numbers of alerts per participant (TERA arm only), and themes from qualitative interview content related to experiences in the intervention will be summarized.

Ethics
The ATN Coordinating Center (UNC-CH) provides sIRB approval, guidance, and monitoring. All clinical research sites and research team institutions ceded regulatory oversight to the Institutional Review Board (IRB) at UNC-CH.

Study and Data Monitoring
On-site monitors from the ATN Coordinating Center will review a selected portion of the individual participant records, including assent/consent forms, case report 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 Protocol Team will review accrual, retention and data quality on monthly team calls, with data combined across study arms. An independent Study Monitoring Committee (SMC) will review the study at scheduled, planned points to monitor participant safety, as well as data integrity. At each review, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide specific operational recommendations to help address any study implementation challenges identified during their reviews. Untoward events will be recorded by the site and reported to the Coordinating Center, study team, and the sIRB.

RESULTS
To date, all clinical research sites have ceded to the UNC-CH sIRB and are in the process of opening for enrollment. First enrollments occurred in April 2018 with a planned 12-month period to reach target enrollment of 120 youth. Participant are followed for 48-weeks, making April 2020 the earliest possible end of data collection. Results are anticipated for last quarter of 2020, potentially early 2021.

DISCUSSION
The TERA study addresses gaps in our evidence-base and interventions for youth and will further the scientific understanding of critical factors in the pathway to ART adherence and success for YLWH on ART. The TERA study will considerably advance scientific understanding of the theory-based dynamics that influence ART adherence. This work advances the number of options for highly generalizable strategies to optimize adherence among YLWH known to have struggled with ART in the past. Interventions that are matched to maturational issues and demands of youth are critically needed. Further, TERA contributes to the understanding of ART adherence and non-adherence in this population at considerable risk for continued ART failure. We are well positioned to advance both science and practice and address ART adherence - a key component of the continuum of care for YLWH. Our research has identified an overall lack of rigorous adherence enhancing research, which has been echoed in a number of recent research syntheses.[5, 23] Evidence for effective interventions for YLWH failing ART regimens is even less well represented in the literature. Although agencies and service providers are advised to adopt evidence-based adherence support strategies, there are no strong, rigorously tested interventions to consider. Three main strategies, well matched to the developmental and social context of YLWH, leveraged in the TERA intervention include electronic dose monitoring with real-time response, engaging youth in a short-term high-intensity program, and centralized adherence coaches.

Electronic dose monitoring, real time triggered interventions, and interactive and real-person phone-based outreach with use of a contact-tree are all novel components to adherence support that promise high impact. The existing evidence base will be leveraged to create a high-intensity, responsive, time-limited intervention approach. While texting has a strong evidence
base for adults[14] [16] [37], use with youth, while intuitively appealing given the widespread use of texting, remains supported largely only by pilot studies.[19] Similarly, phone-based problem solving discussion with adherence coaches has preliminary evidence[20] demonstrated in a pilot study. Our work leverages the wealth of pilot evidence to create an intervention approach with demonstrated promise but not yet rigorously evaluated. Of particular interest, our goal is to mesh together an evidence-informed approach that can also be generalizable. Given that sites and clinics working with youth will have limitations in resources, we adapted interventions implemented over extended period of time to a discreet, intensive approach implemented over a 12-week period and intensified in report to delayed or missed doses. This creates a more generalizable program as resources required are similarly time-limited. The key pieces that make up the TERA intervention are largely in place; YLWH overwhelmingly have cell phones and clinic team members already use or will be trained in problem solving. A system for sending and receiving texts can be automated, with costs allocated towards building the system and minor costs for maintenance of system. If the intervention is effective, it could have an immediate impact on care services provided to YLWH failing ART and future applications to other points in the continuum of HIV prevention and care that depend on youth adhering to the applicable interventions.

Acknowledgements
Supported by the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) from the National Institutes of Health (5U24HD089880-02) through the National Institute of Child Health and Human Development (B. Kapogiannis and S. Lee). Network operations are supported through the ATN coordinating center (University of North Carolina) and data management support is provided by Frontier Science and Technology Research Foundation (FSTRF: Marlene Cooper) and statistical analyses are provided by the Clinical Trials Statistical Data Analyses Center (SDAC: David Shapiro). The authors acknowledge the contribution of the investigators and staff at all participating research sites, and the virtual Youth Advisory Board.

The content in this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of Interest
None declared.
References


42. Amico KR. Standard of Care for Antiretroviral Therapy Adherence and Retention in Care from the Perspective of Care Providers Attending the 5th International Conference on HIV Treatment


### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACASI</td>
<td>Audio Computer Assisted Self-Interviews</td>
</tr>
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<td>ART</td>
<td>Antiretroviral Treatment/Therapy</td>
</tr>
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<td>ATN</td>
<td>Adolescent Medicine Trials Network for HIV/AIDS Interventions</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>EDM</td>
<td>Electronic Dose Monitoring Device</td>
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<tr>
<td>EST</td>
<td>Eastern Standard Time</td>
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<tr>
<td>FSTRF</td>
<td>Frontier Science and Technology Research Foundation</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>IMB</td>
<td>Information, Motivation, Behavioral Skills Model</td>
</tr>
<tr>
<td>IMPAACT</td>
<td>International Maternal Pediatric Adolescent AIDS Clinical Trials Network</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>ITT</td>
<td>Intent-to-Treat</td>
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<td>MI</td>
<td>Motivational Interviewing</td>
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<td>NSC</td>
<td>Next Step Counseling</td>
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<td>RNA</td>
<td>Ribonucleic Acid</td>
</tr>
<tr>
<td>SDAC</td>
<td>Statistical Data Analysis Center</td>
</tr>
<tr>
<td>sIMB</td>
<td>situated-application of the Information Motivation Behavioral Skills Model</td>
</tr>
<tr>
<td>sIRB</td>
<td>single Institutional Review Board</td>
</tr>
<tr>
<td>SMC</td>
<td>Study Monitoring Committee</td>
</tr>
<tr>
<td>SMS</td>
<td>Short Message Service</td>
</tr>
<tr>
<td>SOC</td>
<td>Standard of Care</td>
</tr>
<tr>
<td>TERA</td>
<td>Triggered Escalating Real-time Adherence Intervention</td>
</tr>
<tr>
<td>UNC-CH</td>
<td>University of North Carolina at Chapel Hill</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VLS</td>
<td>Virologic suppression (HIV-1 RNA at &lt;50 copies/mL or &lt;200 copies/mL as specified)</td>
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<tr>
<td>vYAB</td>
<td>virtual Youth Advisory Board</td>
</tr>
<tr>
<td>YAB</td>
<td>Youth Advisory Board</td>
</tr>
<tr>
<td>YLWH</td>
<td>Youth Living With HIV</td>
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