Research Protocol

What strategies are enough to protect youth from HIV:
Automated messaging and self-monitoring, peer social media networks, or interpersonal coaching?

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Abstract

**Background:** The rate of HIV has doubled in the last 15 years among young people to 22% of HIV cases. Scientific advances in biomedical HIV prevention strategies have not been utilized by youth.

**Methods/Design:** Young people aged 12 - 24 years old (n= 1500) are being recruited from community-based organizations (CBO) and clinics serving gay, bisexual, and transgender youth, homeless youth, youth on probation or released from incarceration, and youth in other high-risk venues (e.g., bars and clubs). Youth are randomized in a factorial design to: 1) an automated messaging and monitoring intervention (AMMI) using text messages (n = 900); 2) AMMI plus peer support via private social media (n = 200); 3) AMMI plus strengths-based coaching (n = 200); and 4) AMMI, peer support, and coaching (n = 200). At four-month intervals over 24 months, interviewers monitor: uptake of the steps in the HIV Prevention Continuum (linkage to health care and adherence to pre- or post-exposure prophylaxis or 100% condom use), and conduct repeat rapid diagnostic tests for HIV, sexually transmitted infections (STI), drugs and alcohol use. Weekly automated monitoring via text (or email) in AMMI includes questions on acute HIV and STI symptoms for immediate follow-up by interviewers to provide HIV and STI testing, STI treatment, and partner therapy.

**Discussion:** The greatest impacts are expected among youth receiving the most intensive intervention (i.e., AMMI, peer support, and coach). However, the youth’s concurrent mental health, substance abuse, and housing and food security are expected to be significant covariates that influence the uptake of the HIV Prevention Continuum. This study operationalizes the guidelines of the Centers of Disease Control and Prevention (CDC) regarding the prevention of HIV among the highest risk youth, using community-based point of care diagnostics supported by scalable technology-mediated interventions.

**Trial Registration:** ClinicalTrials.gov registration #NCT03134833, registered April 28, 2017.

**Keywords:** HIV/AIDS, mHealth, homelessness, LGBTQ, MSM, prevention

**Introduction**

America’s HIV epidemic among youth aged 12-24 years old has more than doubled in the last 15 years [1, 2]. Young people now represent 26% of the HIV epidemic [1, 2] despite
investments in evidence-based behavioral interventions (EBI) and more recent scale-up of innovative antiretroviral treatments (ART) that can stop acquisition of HIV known as pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) [3, 4]. Adolescents continue to become infected at disproportional rates [4]. It is critical to intervene with youth at high-risk of acquiring HIV (YAHIR) before they become infected. This study aims to intervene with YAHIR with a set of interventions which could be broadly diffused to stop the spread of HIV. The youth at highest risk for HIV are those in urban epicenters and increasingly in the southeastern United States (U.S.) particularly young Black women, in addition to men who have sex with men (MSM) and transgender youth [1]. YAHIR are difficult to identify in medical clinics because most youth (about 60% of general adolescent population) do not access health care [5-7]. Adolescents typically fail to disclose their sexual behaviors to their families or their physicians, most often because the YAHIR are never asked about risk [8-10]. YAHIR are likely to be encountered at agencies serving lesbian, gay, bisexual, transgender, and queer (LGBTQ) youth; homeless shelters; in the criminal justice system; and through online or in-person venues and events associated with sexual networking [11]. In each geographic epicenter of HIV, YAHIR, especially those who are of Black and Latino ethnicity, are at the highest relative risk of contracting HIV [1, 12]. Homeless youth are also at high risk, yet the last HIV seroprevalence study was conducted in 1991, showing 5.3% prevalence [13]. Youth in the criminal justice system, again over represented with Black youth and substance abusing youth in high prevalence neighborhoods, are YAHIR. YAHIR also typically seek peers, economic opportunities, and social services in the neighborhoods associated with the highest prevalence of HIV such as Hollywood in Los Angeles and the French Quarter in New Orleans.

The current paradigm for reaching global HIV prevention goals (i.e., increased uptake of the HIV Prevention Continuum [14], is far more complex today than in the first 25 years of the epidemic. The U.S. Centers for Disease Control and Prevention (CDC) recommends repeat, routine testing for HIV and STI for YAHIR every three or six months, as well as concurrently linking these young people to HIV prevention and healthcare services and retaining them in care.
over time [15]. This study aims to operationalize these guidelines through enhanced community-based rapid diagnostic testing, referral and linkage, and scalable and flexible technology-based interventions and to evaluate their impact. The possibility now exists to implement biomedical and combination biobehavioral prevention for seronegative youth which requires that youth know their serostatus (i.e., be repeatedly tested for HIV over time), be linked to medical care, and consistently adhere to a strategy to protect themselves from HIV (e.g., high adherence to PrEP, PEP and/or condom use [14]). Table 1 summarizes the multiple endpoints for operationalizing uptake of HIV Prevention Continuum.

### Table 1. The HIV Prevention Continuum for Seronegative GBTY-High Risk Youth

<table>
<thead>
<tr>
<th>Event</th>
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<tbody>
<tr>
<td>Test negative for HIV</td>
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<tr>
<td>Receive healthcare twice annually</td>
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<tr>
<td>Adherence consistently to prevention options</td>
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<tr>
<td>PrEP or</td>
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<tr>
<td>PEP after condomless sexual encounters, or</td>
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<tr>
<td>100% condom use</td>
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<tr>
<td>Repeat HIV and STI testing three times annually</td>
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**Figure 1.** Design of the RCT for YAHR for acquiring HIV (n=1500)
This is a particularly challenging task, since the developmental challenges of adolescence evolve with age, and are likely more difficult for GBTY, homeless, and youth involved in criminal justice. Each of these subgroups is likely to experience discrimination and stigma, especially African American and Latino youth [8, 16-19]. Traditional, in-person delivery strategies for primary HIV prevention may no longer be the most acceptable and feasible strategies to effectively reach and sustain contact with young people to prevent HIV. Disruptive innovations of massively scalable mobile and social media technologies may be able to implement and broadly reach youth with prevention messages and linkage to services [20-22].

Advances in mobile and social media technologies have created opportunities to engage and
intervene with large numbers of youth at relatively low-costs, using technologies that permeate their daily routines [20, 23]. This study will use two primary technology platforms: text messaging and social media, as well as a more traditional in-person and tele-health coaching strategy. We have not created a new mobile application (or “app”) - our experience with smartphone apps indicates that users frequently turn off notification functions, delete apps, and decrease engagement after an initial period of novelty-driven interest declines [24, 25]. App development, maintenance, and updates for new operating system versions is relatively costly and labor intensive. Yet, text messaging, email, and social media use are nearly universal among youth, including homeless youth [26-28]. Rates of mobile phone, smartphone, and internet usage increase with age, and approximately 90% of young adolescents (age 13-17) report having a mobile phone [28-30]. Texting is particularly important for adolescents; 90% of those with phones text, typically receiving and sending 30 texts each day [28]. African American and Latino youth have higher rates of having smartphones as primary access to internet compared to White youth [28, 31]. Ownership, access, and use rates of mobile phones are similar for homeless youth, although with less frequency and some inconsistency [26, 27, 32]. Similarly, over 90% of adolescents under age 18 go online daily, more than half several times a day which is facilitated by access to smartphones among 75% of youth of each ethnicity, crossing the digital divide [28]. Much of this online activity is driven by social media use, particularly via smartphones – for example, over 70% of adolescents under 18 years use Facebook, while about half also use Instagram and Snapchat [28].

The interventions in this study use text messaging and social media to engage “youth where they are” in the digital environment. This approach has resulted in four intervention arms which vary in intensity and costs. In order of increasing intensity and costs, the interventions are: 1) automated text-messaging and weekly monitoring probes; 2) peer support via social media; 3) paraprofessional coaching; and 4) all three combined. This study’s automated and interpersonally-mediated technology-based interventions will be based on the shared features of existing EBI – we will not create a new app nor an EBI with a manual to be replicated with
fidelity [14, 33, 34]. In the last 25 years, over 100 HIV EBI and 36 adolescent sexual health EBI have been identified by the CDC and other review bodies as efficacious [35-37], and supported for diffusion. Across these EBI, no matter the method of implementation, there are highly similar components, processes, and features despite the differences in the “core elements” highlighted by the intervention developers. This team rated the manuals of five of the CDC’s most popular, behaviorally-oriented primary prevention EBI for adolescents [38-40], finding that each incorporated common processes, principles and factors. Each of the EBIs are also based on cognitive behavioral theories, even though some researchers cited a more specific iteration (e.g., social cognitive theory, theory of reasoned action, the AIDS risk reduction model) or meta-theory (e.g., information-motivation-behavior, social action theory). The EBI had much more in common than different [38-41]. This approach has been applied systematically for child and adolescent mental health EBI by the Chorpita, Daleiden, and Weisz research teams with parallel findings [42-45]. In reviewing and rating more than 900 manualized EBIs, they found common practice elements, which they use to guide training and implementation support at scale. The efficacy study evaluating an intervention based on these common elements had an effect size 2.5 greater than the manual-based comparisons [42-45]. In the current study, our intervention approach is to focus on the common elements that many different interventions share, delivered by the most cost-efficient, scalable, and adaptable delivery strategies that permeate adolescents’ daily routines: mobile and social media technologies.

Thus, this is an RCT to evaluate the efficacy and cost-effectiveness of four intervention strategies of variable intensity and cost. Monitoring outcomes at four-month intervals over 24 months, this study aims to inform future prevention programs implemented by communities to avert the acquisition of HIV among young people.

**Automated Messaging and Monitoring Intervention (AMMI)**

Text messaging has been demonstrated to improve ART adherence [26, 46-51], abstinence from drugs and alcohol [52, 53], condom use [54], rates of STI testing and early treatment [55], and HIV re-testing among high risk adults and youth [54, 56, 57]. This team has
also demonstrated efficacy of texting to reduce sexual risk behaviors and substance use with high-risk gay and bisexual men [58-61] and with HRY [55, 62]. Meta-analyses evaluating the efficacy of texting informational, motivational, and resource referral content found benefits for behavior changes when the studies are sufficiently powered [50, 63]. However, most studies are pilots – a major problem in the field of mobile Health (mHealth) [64]. The sample size of this study (n = 1500) is sufficient to test efficacy.

In this study, automated text-messaging is used for both messaging (informational, motivational and referral linkage) and monitoring for symptoms and risks for follow-up testing and linkage. Self-monitoring is a key skill for self-management and a core construct in social cognitive theories [65-67] that has been applied to HIV prevention and self-management interventions. Self-monitoring intervention studies have varied based on the frequency of probes; duration, technology platforms; and diverse software development partners. These studies demonstrate feasibility and acceptability [68, 69], validity and reliability [70, 71], compliance (i.e., protocol adherence) [20, 72], and user-preferences [68, 73]. The efficacy of theory-based mobile self-monitoring to support self-directed self-management has also been demonstrated [70, 74-77].

There is modest meta-analytic evidence for the efficacy of self-monitoring to support change in diet and exercise behaviors to avoid diabetes [78] and obesity self-management [79]. However, self-monitoring has not been widely studied for other health conditions. There is typically a 15% improvement in drug abuse intervention trials when control conditions are repeatedly assessed [80, 81]. Participants recognize the impacts of repeated self-assessments and suggest that more frequent assessments might result in greater effects [80]. Self-monitoring by mobile or web-apps also suggest motivational interviewing to reduce substance use and sexual risk are effective with substance users, persons living with HIV and at high-risk for HIV infection [82-87]. Recent pilot studies by our team found that coaches using web-based dashboards to monitor clients' progress and facilitate coaching were highly acceptable, enhanced bonds and accountability, and enhanced efficacy of a small group intervention to
reduce methamphetamine use and sexual risk behaviors among gay and bisexual men [75, 88].

When mobile health tools are used in supportive relationships, as in a peer support and coaching intervention arms in this RCT, there may be synergistic effects based on the concept of supportive accountability [89]. If AMMI are efficacious, this will provide a relatively low-cost and scalable intervention that could be diffused nationally.

**Peer Support via Social Media**

Peer Support is a low-cost strategy to enhance prevention and adherence interventions. Relationships have been shown to be motivating and increase engagement and retention in care for a range of chronic diseases [90-92]. Almost every EBI for HIV prevention and treatment on the CDC’s Compendium of EBI has a peer support component [93]. Yet research to confirm the efficacy of peer support has varied widely. A recent meta-analysis of more than 31 RCTs using electronic peer support did not find significant benefits for peer-to-peer interventions alone [94]. Similarly, Simoni [95] did not find that in-person peer support groups enhanced ART adherence. However, a review published in 2014 found significant benefits of peer support interventions for other chronic diseases [96]. In a review of stress management interventions for persons living with HIV [97], peer support was a critical component of interventions. In addition, two peer support interventions with men who have sex with men conducted via Facebook groups over twelve weeks found increased requests for HIV home test kits in Los Angeles [98] and increased clinic-based HIV testing in Peru [99]. Similarly, Reback and colleagues [59, 100] found that peer support via text messaging for eight weeks reduced substance use and sexual risk behaviors among methamphetamine-using men who have sex with men. Adolescence, in particular, is a developmental period where the influence of peers is crucial [101]. Based on these considerations, this study will test the efficacy of peer support via social media over 24 months.

**Coaching for HIV Prevention**

“Patient Navigators” are one of the primary strategies advocated to link and retain high-risk populations to prevention and treatment services. Similar to navigators used for other chronic diseases [102-104], the CDC recommends patient navigators can help optimize the HIV
Patient navigation involves a paraprofessional or experienced peers helping persons link to healthcare, assist with insurance, problem solve barriers to care, and provide supportive counseling to motivate engagement and retention in health services. In this study, we use “coaches” who initially engage youth in person and then primarily use electronic means of communication and interaction (e.g., texting, private messaging through social media platforms, email, voice calls, video chats). The focus of all contacts is linkage and retention in the HIV Prevention Continuum. In addition, coaches aim to address the hierarchy of needs undermining prevention outcomes, such as homelessness, employment, mental illness and substance abuse.

Consistent access and utilization of medical care is a common challenge for adolescents and young adults [107], particularly African American and Latino youth [108]. From the ages of 18-24 years, about 30% of youth do not have any health insurance [109, 110], even with the Affordable Care Act [111]. Between the ages of 12 to 17 years, adolescents typically have one medical appointment for illness and no preventive healthcare visits [7]. In fact, adolescents do not seek medical care about 40% of the time when they are sick with physical symptoms [5-7, 108].

Coaches must encourage YAHR to consider PrEP and PEP interventions and linkage and retention to medical care. The coaching condition aims to provide this more intensive support for healthcare linkage necessary for PrEP and PEP, as well as for addressing mental health, substance abuse, sexual health, homelessness, and employment.

The coaching intervention condition provides two levels of intervention engagement to meet the needs of diverse YAHR with varying preferences and needs for intervention engagement: a) prevention service linkage navigation and b) strengths-based client-centered coaching [112]. Participation is highly variable among youth in interventions [58, 113, 114]. Many participants perceive little need for intervention support, while others are highly engaged and want many contacts. Participation often increases when a crisis precipitates a shift in perceived needs for support. The pervasive use of social media for communication by youth currently has
reinforced the lack of necessity for face-to-face communication and preferences towards text-based communication (via social media apps and text messaging). For some, trauma and mistrust of service providers or researchers adds further layers of barriers (e.g., discomfort) to engaging in coaching or counseling relationships. Coaching support might build rapport and trust in small steps over time using youth’s preferred methods of communication and relationship building, which may then reduce barriers to engaging in more intensive coaching support is needed.

Methods/Design
All procedures in this study have been approved by the Institutional Review Board (IRB) of the University of California, Los Angeles, which serves as the single IRB of Record for researchers at collaborating institutions: Tulane University, University of California, San Francisco, Columbia University, University of Central Florida, Nova Southeastern University, and Friends Research Institute.

Recruitment Sites. In both Los Angeles and New Orleans, the Recruitment, Engagement and Retention Centers (RERCs) are responsible for recruiting, enrolling and following-up with youth. Youth are primarily recruited from CBOs and clinics serving gay, bisexual, and transgender youth, homeless youth, youth on probation or released from incarceration, and youth in other high-risk venues (e.g., bars and clubs).

This study aims to screen up to 4,500 youth across Los Angeles and New Orleans to identify 1,500 seronegative YAHR of contracting HIV. We anticipate this cohort to be predominantly MSM and transgender youth, largely African American and Latino, aged 12-24 years old, and the majority will fall between the ages of 18 and 24 years of age. We anticipate a higher proportion of women in our sample from New Orleans and that while most youth from New Orleans will be African American, youth in Los Angeles will also be Latino and White and predominately GBTY. Further details on each of the ATN CARES studies may be found in the corresponding study protocol papers [112, 115-118].

Recruitment Process. Two teams of predominantly Bachelor’s-level Interviewers are recruiting the cohort. Recruitment is proceeding in two steps. First, youth in high-risk settings
are approached with a brief Screener and rapid HIV test. For youth aged 15-24, they are asked to provide oral consent to screen. For youth aged 12-14, they are asked to provide written voluntary informed consent to screen. To screen as “eligible” for enrollment in the study, youth must test seronegative on a rapid HIV test and report at least three high-risk criteria: self-reporting as GBTY; Black/African American or Latino race/ethnicity; having unprotected anal sex, sharing needles for injecting drugs, or any other potential HIV exposure in the last 12 months; having been homeless (defined as not having a regular place to sleep for three or more months); illicit substance use (not including marijuana) in the last 12 months; having been hospitalized for a mental health disorder; having been in jail or on probation; or, having a STI in the last 12 months. Any seronegative youth who self-identifies as transgender or reports current PrEP/PEP use is automatically eligible. Based on these screening criteria, eligible youth are invited to complete voluntary informed consent and are randomized to intervention conditions by a computer-generated algorithm in the field.

As part of the voluntary informed consent procedures, youth are asked to provide consent for access to sensitive information for care coordination and study retention for the duration of the study (24 months). This includes their contact information, social media accounts, the contact information of their close relatives, friends, and providers, including case managers and probation officers, as well as their social security number, driver’s license or identification card number, their facial photo or image, and access to their medical records and location through a social security.

Assessments. Following recruitment, study participants are asked to complete a baseline assessment, which includes a questionnaire and a series of rapid diagnostic tests (RDT). The following RDT are performed (see Shannon et al., this volume).

- HIV – as part of screening, potential study participants undergo HIV testing using the CLIA-waived Alere Determine HIV-1/2 Ag/Ab Combo fingerstick blood test for both HIV-1/2 antibodies and the HIV-1 p24 antigen with a window period of 12-26 days, which can be read in 20-30 minutes. Once enrolled in the study, participants also receive HIV
testing using the Cepheid Xpert HIV-1 Qual Assay, which is highly sensitive and uses whole blood to detect HIV-1 total nucleic acids and has a 90-minute read time.

- Chlamydia and Gonorrhea – are tested using FDA-approved Cepheid Xpert CT/NG Assay PCR test using vaginal swabs from women, urine samples from men, and pharyngeal and rectal swabs from both women and men. Results are read in 90 minutes.

- Syphilis – is tested using the CLIA-waived Syphilis Health Check fingerstick blood test to detect treponemal antibodies with a 10 to 15-minute time to completion.

- Hepatitis C – is tested using the CLIA-waived OraQuick HCV Rapid Antibody test fingerstick blood test with a 20 to 40-minute read time.

- Substance Use – is tested using a multi-drug urine test panel to detect the presence of marijuana, cocaine, opiates and methamphetamine with a 2 to 5-minute read time.

- Alcohol Use – is tested using the BACtrack breathalyzer to determine blood alcohol content (BAC) over the past 48 hours.

Following completion of the baseline assessment, participants receive a $50 cash incentive. Any study participants who test positive for HIV are immediately linked to care for treatment and enrolled in one of the ATN CARES protocols for youth living with HIV, depending on stage of HIV infection determined by Fiebig stages I to VI on HIV-1 antibody using Western blot test. Participants testing positive for other STIs are provided immediate treatment by the study team, including partner therapy.

The baseline assessment is interviewer-administered using Android tablets in approximately 45 minutes. This assessment covers the following domains: sociodemographic factors; healthcare access, insurance, and utilization; substance use, sexual activity; PrEP and PEP; mental health; and communication and social media. Within these sections, there are eight cross-cutting domains related to the HIV Prevention Continuum, which include: HIV and STI testing; healthcare – both having insurance and a regular provider; previous participation in an HIV prevention program; consistent condom use; concurrent sexual partnerships; and PrEP and PEP awareness, use, and adherence.
Interviewers enter the participants’ responses in the CommCare system developed by Dimagi Inc., a mobile health company. CommCare is an open-source, mobile phone-based platform that is cloud-based and HIPAA-compliant. The CommCare mobile application is being used to collect data by both the assessment and the intervention teams, including screening, assessment and intervention data, as well as contact and locator information. CommCare is also responsible for sending out text-messages and surveys as part of AMMI.

**Follow-up Assessments.** Study participants are reassessed every four months, over a period of 24 months. In total, study participants complete six follow-up assessments and receive a $50 cash incentive for each follow-up assessment. Follow-up assessments will include another 45-minute assessment and series of RDTs for HIV, STI, and substance use, as described above. In addition, if study participants report any potential acute HIV symptoms or exposure, or STI symptoms or exposure in weekly monitoring text message or email surveys, they are immediately offered testing and referral to PEP, in case of HIV exposure.

**Outcome Measures.** Our primary outcome is uptake and adherence to the HIV Prevention Continuum, according to the following measures:

1. Linkage to medical care reflected in a visit twice annually, at a minimum, to a health care provider;
2. Consistent utilization of condoms, PrEP or PeP;
3. Repeat assessments for HIV and STI testing three times annually.

Secondary outcomes include:

1. Mental Health Symptoms. Participants self-report symptoms of anxiety and depression at baseline, four-month assessment points and weekly check-in surveys.
2. Substance Use. RDTs for alcohol, marijuana, methamphetamines, opiates and cocaine measure substance use at baseline and four-month assessment points. The AUDIT-C, which measures problematic alcohol use, is also administered as part of study
assessments. Lastly, participants self-report substance use on weekly check-in surveys (i.e., number of days using drugs or alcohol in last week).

3. Housing Insecurity. Participants self-report housing insecurity at baseline, four-month assessment points, and on weekly check-in surveys.

Routine Costing Data. There are two types of costs: costs of delivering the intervention and additional costs incurred by participants for their use of healthcare services and services from other agencies (e.g. use of healthcare services). Intervention costs are classified into one of four categories [119]: 1) Capital equipment (e.g., computers); 2) recurring supplies and services; 3) facility space; and 4) personnel, including fringe benefits. Costs in the first three categories are obtained from project records. Personnel costs include hours and wages of staff to design and deliver the interventions, including peers, coaches, supervisors, facility charges, software costs, and SMS and other social media costs, messaging and mobile application data costs, additional time in coaching and supervision, and server hosting. Personnel time is estimated from several sources. Time reported on time sheets, for hourly employees, and budgeted time provide a basis for each staff member’s hours devoted to the project. Time for hourly staff (e.g., coaches and interviewers) will also be validated using an activity reporting system. Staff were given Android phones for study activities. Each staff member records study activities for week-long time periods throughout the study period using the Android mobile app, Time It [120]. Recorded time over one-week periods are extrapolated to cover total time over the study period. The costs of additional services are derived from respondent reports on utilization, medical records, and are estimated using publicly available data. Research-specific costs, such as incentive payments, informed consent, screens, and software adaptation for survey tools, are excluded from total costs. All cost data are price-adjusted back to year one of the study, using the medical care component of the consumer price index.

Intervention Development. Consistent with the model of community-based participatory research [121, 122], Youth Advisory Boards (YAB) of seronegative high-risk youth
have been recruited in each city and reflect the diversity of the youth to be recruited in both Los Angeles and New Orleans, with representation from all ethnic groups. Each YAB is comprised of approximately 10 members. The YABs are involved on an ongoing basis to ensure that we continuously improve the interventions. The YAB provides feedback and informs details of the study procedures, assessments, and interventions. In particular, YABs have adapted libraries of existing text messages for project launch and provided topics of interest for peer support discussion boards. In the coming months, YABs contribute to ongoing text message and peer support discussion board development to keep content fresh and updated for the 24 months of intervention delivery and follow-up.

The existing libraries of theory-based HIV prevention messages adapted by the YAB include: 1) Project Tech Support [60] which has developed over 500 theory-based text messages specifically for high-risk MSM focused on reducing sexual risk behaviors and substance use, tailored to risk profile information (e.g., serostatus, adherence, injection drug use); 2) the UCARE4LIFE text messaging library from the HRSA HIV/AIDS Bureau [123]; and, 3) PrEPTech from youth+tech+health (YTH) focused on increasing uptake and adherence to PrEP [124]. These libraries formed the basis of the initial message content for adaptation in collaboration with the YABs, which will continue throughout the study duration. Message libraries have been tailored for two different risk profiles - LGBTQ and heterosexually-identified youth. Research indicates that messaging interventions based in cognitive-behavioral theory are more likely to be successful [125-128]. The adapted message libraries were based on Social Support Theory [129-131], the Health Belief Model [132-134] and Social Cognitive Theory [135, 136].

**Intervention Conditions to Optimize the HIV Prevention Continuum**

**Condition A: Automated Messaging and Monitoring Intervention alone (AMMI; n = 900).**

Text messages aim to: 1) motivate, inform, and refer youth to services once daily; and, 2) monitor weekly seven domains related to the primary and secondary outcomes. This
intervention is provided to all study participants across study arms as part of an enhanced standard of care.

**Daily texts to motivate, inform, and refer youth to services.** Messages are sent daily, at a time selected by the participant, which can be updated at each four-month re-assessment. Some evidence suggests that several text messages each day might be required to have an impact on behavioral outcomes [58, 59, 100]; therefore, up to five messages are sent per day, which youth may opt-out of and opt-into at any time during the study. Messages related to healthcare, wellness and medication reminders (i.e., if taking PrEP) are sent on a daily basis. Messages related to sexual health and drug use are sent on Thursdays, Fridays and Saturdays a design decision based on YAB guidance to minimize messaging burden for these sensitive topics while maximizing impact on days when risk behaviors are most frequent.

**Monitoring weekly in seven domains.** Our monitoring strategy is based on a weekly “Check-In” survey, which can be completed via text message or web link sent via email with a link to a HIPAA compliant Red Cap version of the survey. “Check-In” surveys assess select domains of the HIV Prevention Continuum as shown in Table 2. Youth receive an incentive of $1 per weekly survey completed.

<table>
<thead>
<tr>
<th>Table 2. Automated Messaging and Monitoring Intervention (AMMI) Daily Text Message Examples</th>
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<tbody>
<tr>
<td><strong>Healthcare</strong></td>
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<tr>
<td><strong>Wellness</strong></td>
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<tr>
<td>Gay Pride is taking care of yourself.</td>
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<td>--------------------------------------</td>
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<tr>
<td>Been inside all day? Get outside and soak up some quick sun for a boost of energy.</td>
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<thead>
<tr>
<th>Sexual Health</th>
<th>If your partners wants to get tested for HIV, text KNOWIT (566948) and enter their ZIP code. KNOWIT will text back a nearby testing site.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left untreated, some STIs can cause health problems that make it hard or impossible for a woman to get pregnant. Visit <a href="http://1.usa.gov/1dm9P0B">http://1.usa.gov/1dm9P0B</a> to learn more.</td>
</tr>
<tr>
<td></td>
<td>Open relationship? Know your boundaries.</td>
</tr>
<tr>
<td></td>
<td>Make sure the only thing you “get” is laid.</td>
</tr>
<tr>
<td></td>
<td>Friction is the enemy. You can lube up every time.</td>
</tr>
<tr>
<td></td>
<td>Myth: Women can't give men HIV. Fact: Both men and women can get HIV from vaginal and anal sex.</td>
</tr>
</tbody>
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<tr>
<th>Drug Use</th>
<th>Stay in control—people who are drunk or high take more risks.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>When was the last time you had sex sober?</td>
</tr>
<tr>
<td></td>
<td>Drinking alcohol can take a toll on your body. Take care of you!</td>
</tr>
<tr>
<td></td>
<td>Only take a fixed amount of cash out (and no cards) if you want to control how much you drink.</td>
</tr>
<tr>
<td></td>
<td>Spending too much money on Tina?</td>
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</tbody>
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<thead>
<tr>
<th>Medication Adherence</th>
<th>Reminder. It's going to be a great day. When you take your meds regularly, you're in control.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>It's that time again.</td>
</tr>
<tr>
<td></td>
<td>Take care of yourself today.</td>
</tr>
<tr>
<td></td>
<td>Is your stomach feeling a little off after taking your PrEP? Try taking your pill with food to ease possible stomach discomfort.</td>
</tr>
<tr>
<td></td>
<td>Where are you storing your PrEP? Your hot car or fridge can damage the medication—keep it at room temperature.</td>
</tr>
</tbody>
</table>

Surveys remain open for response for 48 hours. In the case of non-response, CommCare automatically sends a follow-up prompt 24 hours after the initial prompt. After 2
weeks of non-response, RERC interviewers initiate follow-up to assess current status of the youth. Reports of potential acute HIV or STI symptoms are provided to the RERC interviewer teams on a weekly basis for immediate follow up for HIV or STI testing.

**Condition B: Peer Support via Social Media plus AMMI (n=200)**

Participants randomized to Peer Support via Social Media (in Conditions B and D) are invited to participate in a private online discussion board through www.Muut.com. Muut is an open-source discussion platform that is mobile and desktop-friendly. Users can personalize their Muut profiles using avatars and photos, and content created can be continually reorganized according to new and relevant “channels” (e.g., for a PrEP channel, mental health-related channels). Participants are required to register and request access to join, which is facilitated by detailed screenshot introductions sent by SMS and in-person by coaches at the recruitment sites. Coaches and project coordinators review access requests to ensure that only participants are attempting to join the board, and that their usernames do not compromise their anonymity by including their names. As enrollment continues and participation increases, separate forums may be established for sub-groups of youth based on sexual orientation, gender identity, or age (e.g., for below/above 18 years, for participants who identify as transgender) but initially, we want to ensure enough participants in each discussion board to stimulate and maintain conversations.

Coaches and intervention coordinators moderate the boards throughout each day to ensure that ground rules are followed, delete inappropriate posts, post correct information, and credit incentives for participants. Users are removed from the discussion board if they post inappropriate content three times after receiving feedback for each occurrence, which includes: solicitations for sex and drug use; racist, homophobic, or other stigmatizing content; pornographic content; “trolling” inflammatory remarks or personal insults. Participants can communicate with each other by expressing their thoughts on posts made by coaches and/or other participants, creating their own posts, and sharing experiences and advice on HIV Prevention Continuum themes: PrEP, PEP, and condom use efficacy, availability, and
adherence; importance of repeat testing for HIV and STIs, their symptoms, immediate STI
treatment and HIV testing, if potentially experiencing symptoms of acute infection, and locations
of services. Then coaches prioritize themes of comorbidities of substance abuse, mental health,
housing and food insecurity; the importance, value, and availability of services, treatment, and
support from trusted family and friends. Many of these themes may also come up
spontaneously in discussion and posts – the protocol is simply a checklist of the above themes
to guide coaches in the initiation of content.

**Condition C: Coaching plus AMMI (n = 200)**

The coaching condition represents the most intensive person-mediated strategy in this
study. However, the coaches can use telehealth modes of communication and interaction (e.g.,
using text messaging, social media private messaging, phone calls, video-chat, email) in
addition to in-person meetings and sessions. In-person contacts are accommodated to initiate a
coaching relationship and on an ad-hoc basis at recruitment sites and/or to accompany to
appointments as needed (i.e., when virtual support fails) and feasible (less than one-hour drive).
Details of the functional priorities are listed below, but in short, this is not a sequenced session-
based model.

Coaches focus on the following priorities in their contacts with youth:

- Crisis support to address youths’ immediate priorities and needs, particularly
  housing, which are typical barriers to engaging in other health promoting activities;
- Completion of a strengths-based assessment session, including goal setting;
- Problem solving priorities and facilitating linkages to prevention services, healthcare,
  and other services and providers (e.g., Case Managers at recruitment sites, nearby
  agencies, or providers for mental health, substance abuse, housing, jobs, school, in
  conjunction with Case Managers, if available);
- Appointment coordination, scheduling, and reminders;
- Follow up to clients for rewarding attending appointments or problem solving for
  missing appointments.

Coaching is based on the strengths-based model [137], which has demonstrated
positive impacts with persons living with HIV [138] and for HIV prevention. Identifying and
accomplishing goals are critical components of the model. The strengths-based assessment addresses six main life domains: 1) daily living (survival needs such as food, housing, finances, employment); 2) physical health (non-HIV related health problems); 3) healthcare (insurance enrollment); 4) social relationships (including social support, disclosure, stigma); 5) mental health; and 6) risks (substance use, risky sexual behaviors). Youth are asked to identify their current status within each domain, as well as strengths and challenges in each area.

This assessment guides the development of personalized goals. Each youth has a maximum of three goals at any given time. The coach and youth identify a primary goal to address following the session including identification of resources, as well as skills needed to achieve the goal (e.g., problem-solving, coping skills). Typically, long-term or lofty goals must be broken down into "SMART" goals (i.e. specific, measurable, achievable, realistic, and timely). Responsibility for goals is shared between the youth and coach depending on the nature of the goals. At each subsequent session, the coach “checks in” with the youth on goals set in previous sessions. As goals are accomplished, new goals are set. Goals not met are problem-solved and adjusted to be achievable in successive approximation.

After every contact with a participant, whether a full coaching session or brief, the coach completes a brief, mobile-web-based set of questions in CommCare asking for content areas covered, the coaching skills used, and the perceived benefit to the participant. This activity logging functions to prompt coaches to use the skills and address the content priorities of the intervention while simultaneously providing process data for analyses and to inform supervision.

Training and Supervision. Coaches are experienced Bachelor’s-level paraprofessionals, recruited in collaboration with study sites. In addition to the components of the strengths model, coaches are taught the foundational theory of behavior change (people change slowly over time with small steps and with opportunities and rewards), the shared principles of behavior change (Be Prepared; Act on facts, not feelings); and 17 skills common to 80% of all child and adolescent EBI [45, 139] including: engagement/rapport expectations, self-monitoring, goal
setting, praise, problem-solving, setting up rewards, support networking/build social support, monitoring, emotional regulation, positive self-talk, triggers, modeling/roleplaying, assertiveness communication, referrals, positive activities/alternatives, relapse prevention, and relaxation. These skills are repeatedly drilled with all coaches as their toolbox for addressing the core content areas to be address: daily living, health, social relationships, mental health, anxiety, depression, crisis, violence, sexual behaviors/condom use/PEP or PrEP, substance abuse, antiretroviral adherence, HIV, other. The existing EBI modules are practiced as prototype models that could be adapted and tailored by the coach for the specific YLH they are supporting.

Coaches participate in weekly, cross-site supervision via in-person and video-conference meetings to debrief and jointly problem-solve logistical and clinical challenges with the Principal Investigator and Project Directors. In both Los Angeles and New Orleans, there are local, on-call clinical psychologists for participants in crisis and who also provide weekly clinical supervision and ongoing booster training to Coaches.

**Condition D: Peer Support via Social Media, Coaching plus AMMI (n=200)**

This intervention condition (n = 200) delivers the combination of the above interventions, which enables estimation of the cumulative or synergistic effects of what might be considered an ideal model of support for high-risk seronegative youth to optimize their engagement and retention in the HIV Prevention Continuum.

**Data Analysis**

Analyses are described according to each of the study aims.

**Aim 1: To Assess the Independent and Synergistic Effects of the Interventions on the HIV Prevention Continuum Outcome.**

Multilevel models (MLM) will be used to test the impact of the intervention on HIV prevention continuum indicators shown in Table 1 and secondary outcomes, such as mental health and drug use measures, over time. MLM are needed to account for the hierarchical nature of the data and model correlations between repeated observations in order properly estimate standard errors on regression coefficients. MLM are flexible in handling discrete
outcomes, such as binary HIV-prevention-continuum indicators (yes/no) and continuous outcomes, such as mental health measures. The MLM analyses will contain main effects for peer support (PEER\textsubscript{i}) and coaching (eNAV\textsubscript{i}), as well as a two-way interaction between peer support and coaching compared to AMMI alone. This model parameterization will allow us to test independent effects of peer support and coaching and their synergistic effects on outcomes. MLM contain interactions between TIME and intervention effects to test for changes in outcome levels between intervention arms over time (our primary goal). Equation 1 shows a random intercept (RI) model that will provide a starting point in the modeling process. Let \( Y_{it} \) be an outcome for person \( i \) at time point \( t \) and let \( \eta_{it} \) be a link function for outcome \( Y_{it} \), such as a logit link for binary prevention-continuum indicators. A MLM with random effect \( \lambda_{i} \) to capture correlations between repeated observations for each person is expressed as

\[
\eta_{it} = \beta_0 + \beta_1 \text{PEER}_i + \beta_2 \text{eNAV}_i + \beta_3 \text{TIME}_{it} + \beta_4 (\text{PEER}_i \times \text{TIME}_{it}) + \beta_5 (\text{eNAV}_i \times \text{TIME}_{it}) + \beta_6 (\text{PEER}_i \times \text{eNAV}_i \times \text{TIME}_{it}) + \lambda_i. \quad \text{(Equation 1)}
\]

We will also fit MLM with other covariance structures that we have used in prior HIV studies, including random intercept and slope (RIAS) and autoregressive covariance structures. The covariance structure with the best fit statistics will be selected. Covariates for demographics and other background characteristics may need to be added to Equation 1 if imbalances are found across intervention arms at baseline.

As a first step, MLM will be fit to each primary and secondary outcome and intervention effects for each outcome will be evaluated separately. We will also evaluate the overall impact of the intervention across binary indicators for optimization of the prevention continuum utilizing a strategy employed by this team to analyze multiple outcomes with one overall statistic, to reflect if there is an overall impact on multiple binary outcomes \[140\]. Analysis of multiple outcomes through separate regressions increases the probability of finding a significant intervention effect by chance (i.e., Type I error is inflated). Therefore, we will properly adjust the Type I error by
conducting simulation studies to determine how many significant intervention effects are needed to declare an effective intervention. Simulation studies assume binary outcomes to be correlated to model real world phenomenon.

**Aim 2: To Assess the Temporal Relationships Between the Primary and Secondary Outcomes.**

The temporal relationships between primary and secondary outcomes will be analyzed using bivariate-outcome MLM to examine bidirectional relationships between primary and secondary outcome observations at different time points. One parameterization of the bivariate-outcome MLM that we have used in a prior HIV study to examine the time-varying relationship between HIV-transmission behaviors and mental health symptoms is the bivariate RIAS model [141]. This model is formulated through two separate MLM equations for each outcome, \( k = 1, 2 \), that are linked through random effects to model random intercepts \( \lambda_{0ki} \) and slopes \( \lambda_{1ki} \). A covariance matrix is also modeled that includes correlations between random effects \( \lambda_{0ki} \) and \( \lambda_{1ki} \). Correlation between random effects captures time-varying associations between outcomes, such as the correlation between the first outcome at baseline and the second outcome over time, and vice versa. Building on Equation 1, the basic bivariate RIAS model is expressed as

\[
\eta_{kit} = \beta_0 + \beta_1 \text{TIME}_{kit} + \lambda_{0ki} + \lambda_{1ki} \text{TIME}_{kit}.
\]

(Equation 2)

**Aim 3: To Assess the Relative Cost-Effectiveness of the Interventions.**

The deployment of all HIV prevention strategies today must be based on the cost-effectiveness of peer-support and coaching to automated messaging for HIV prevention continuum outcomes and reducing risk behaviors, substance use, and mental health problems. The cost-effectiveness analysis will compare the additional cost required, on average, to get an additional unit of outcome in the two person-mediated interventions (peer-support and coaching)
and in the attentional control (automated messaging) by calculating a Cost Effectiveness Ratio (CER) [142]. The CER is the difference in total costs of providing a person-mediated intervention versus automated, divided by the difference in outcomes of person-mediated and automated [142]. Primary outcomes of HIV prevention continuum, and secondary outcomes of risk behaviors and co-morbid substance use and mental health, are outcomes of interest. Costs are measured as described above.

$$\text{CER} = \frac{C_{\text{person}} - C_{\text{auto}}}{O_{\text{person}} - O_{\text{auto}}}$$

Analogous CERs will be calculated for peer-support versus automated/attentional control, patient coaches versus automated, and for the combined peer-support and coach versus automated control. CERs will be calculated at final follow-up. We expect the person-mediated interventions to incur greater personnel costs than the automated. On the other hand, the person-mediated interventions may result in greater users of other mental health or drug treatment services than the automated group. These greater costs may or may not be offset by reduced costs of other services, such as incarceration, relative to the person-mediated groups. The CER answers the question of whether improvements in outcomes are worth any added costs. If the person-mediated interventions result in both better outcomes and lower net costs, it will be deemed “cost-saving”.

We conduct sensitivity analyses, as recommended by Gold et al.,[142] to estimate the extent to which the CER calculation is affected by differences in assumptions about the size of the differences in treatment effect. In particular, we determine how sensitive the CER is to assumptions that the difference in treatment effect is 1 standard deviation below or above the mean estimated effect size. Similarly, we estimate the sensitivity of conclusions to costs that are 1 standard deviation below or above the estimated mean.

**Sample size calculations.** Sample size calculations are conducted to detect changes in the probability of an HIV care continuum yes-no indicator, such as PrEP adherence, STI treatment, and 100% condom usage, over 7 time points (every 4 months over two years). Calculations show that we have at least 80% power to detect differences in the probability of an indicator as
small as 8% to 11% at the last time point between the AMMI Arm (n = 900) and any of the remaining three Arms (n = 200), including the peer support + AMMI, coach + AMMI, or peer support / coach + AMMI Arms. We will be able to detect differences in the probability of testing as small as 10% to 16% at the last time point between two Arms with 200 participants. Sample size calculations were conducted through simulation using the following steps. First, binary indicator values were simulated from a binomial distribution with the probability of an event (yes) based on a MLM similar to Equation 1. Simulation regression coefficients were specified with baseline rates of 20%, 50%, and 80% to cover a range of care continuum rates we have encountered in prior HIV research and were set to be the same between intervention Arms. We specified normally-distributed random effects as we did in Equation 1 with a standard deviation of 1.5, similar to what we have found in other studies. Lastly, we assumed 20% loss to follow-up and used a sample size of 720 for the AMMI Arm and a sample size of 160 for the remaining Arms in simulations. In practice, we anticipate a much lower attrition rate, but wanted to be conservative in our sample size calculations. We simulated 1000 data sets for each of the baseline testing rates we specified and for different sample sizes for two-Arm comparisons (either 720 and 160 or 160 and 160). Second, we fit MLM models to each of the 1000 simulated data sets for differing combinations of parameters. Lastly, power was estimated to be the ratio of the number of MLM with a significant difference between intervention arms over time divided by 1000.

Discussion
Text-messaging and social media technologies offer relatively low-cost modalities to scale interventions for all adolescents nationally. Our design provides opportunities to assess the efficacy, potential synergistic or cumulative effects, and cost-effectiveness of the proposed automated and person-mediated strategies, which will enable examination of time trends, periodicity of risk, intervention effects, and bivariate outcome analyses. In our evaluation of each intervention condition’s cost-effectiveness for the primary outcome we hypothesize that peer support and coach arms may have greater efficacy compared to AMMI alone, but that their
added costs for peer incentives, coaches, and their training and supervision may not justify use at scale.

The mobile and social media intervention arms in this study build off the relatively nascent evidence-base of internet, mobile, and social media interventions for populations at high risk for acquiring or transmitting HIV [143-147]. Although technology-based assessments studies (e.g., web-surveys) [144, 148] have demonstrated success with large samples in the thousands [149], mobile and social media technology interventions studies have tended to be smaller scale by comparison [64]. While several R01 scale RCTs are currently underway, most focus on a single technology-based strategy or a bundle of strategies in a single intervention arm, instead of a comparison of multiple strategies as proposed in this study [147, 150, 151].

Youth present with a wide variety of issues that affect their risk for HIV infection. In addition, they can be extremely labile in terms of their emotional and behavioral reactions to life events as they undergo developmental changes, which affects their risk. Rather than one “set” or “fixed” intervention, this study was developed to determine the “amount/dosage” of different intervention methods that would be effective for youth: automated messaging and monitoring intervention (AMMI) using text messages; AMMI plus peer support via social media; AMMI plus a coach; and AMMI, peer support, and coach. These data allow an in-depth analysis of which youth work within each level(s) of intervention. In order to assess cost-effectiveness, this type of data is critical: how do we control costs for prevention while still having a significant impact on risk reduction that actually works in terms of lower costs for these youth? This study both combines and bridges some of the intervention methods that could or should be effective for youth in a way that allows analysis of the effectiveness of the different combinations of intervention methods.

A greater understanding of temporal relationships between changes in prevention and psychosocial comorbidities will inform the development of future HIV interventions. Traditional analytic approaches, such as regression models, require an outcome and predictor(s) to be specified, that is, an a priori relationship is assumed between measures ahead of time. This
approach does not suffice to examine temporal relationships between measures over time. Instead we will use bivariate-outcome models as an innovative method that will allow us to examine bidirectional relationships between primary and secondary outcome measures over time in the intensive longitudinal data. This same approach can also be applied to the 4-month follow-up testing and self-report data. We have developed and used bivariate-outcome models in prior studies [141, 152-155]. For example, we examined temporal relationships between HIV-transmission behaviors and mental health symptoms in a study of HIV-positive adults.[141]. Another benefit of this study is the data that can inform future studies, such as effectiveness of the weekly “check-in” survey prompts by text message and immediate follow-up for testing and treatment, discussion board interactions, and coach contacts. These findings are invaluable for future adolescent studies in not only HIV, but also in other many other areas of outreach and intervention.

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Conflicts of Interest
The authors declare no conflicts of interest.

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