Research Protocol

Moving Toward a Cure: Integrating the Care and Prevention Continua to Stop HIV in the United States for Adolescents and Young Adults

Mary Jane Rotheram-Borus, Ph.D.,¹ M. Isabel Fernandez, Ph.D.,² Sung-Jae Lee, Ph.D.,¹ Sue Ellen Abdalian, M.D.,³ Leslie Kozina, R.N.,³ Maryann Koussa, M.P.H.,¹ W. Scott Comulada, Dr.Ph.,¹ Jeffrey Klausner, M.D.,⁴ Elizabeth Mayfield Arnold, Ph.D.,⁵ and Dallas Swendeman, Ph.D.¹

¹Department of Psychiatry & Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA
²College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL
³Department of Pediatrics, School of Medicine, Tulane University, New Orleans, LA
⁴David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA
⁵Center for Behavioral Health Research and Training, School of Social Work, University of Central Florida, Orlando, FL

Corresponding author: Mary Jane Rotheram-Borus
10920 Wilshire Blvd., Suite 350, Los Angeles, California 90024 USA
Tel: +1 (310) 794-8278   Fax: +1 (310) 794-8297   Email: CCHPublications@mednet.ucla.edu
Abstract

**Background:** The United States is experiencing a growing HIV epidemic among youth aged 12-24. Yet, youth have the lowest rates of antiretroviral (ARV) uptake and adherence, indicating a need for novel community-based strategies to optimize the HIV Prevention and Care Continua. We have designed a set of inter-related studies to operationalize the guidelines of the Centers for Disease Control and Prevention (CDC) for youth living with HIV (YLH) and youth at highest risk (YHR) of acquiring HIV and to test three interventions of varying intensity.

**Methods/Design:** Gay, bisexual, and transgendered youth (GBTY), homeless youth, substance-abusing youth, youth with criminal justice contact, and youth with significant mental health challenges, particularly those who are Black and Latino youth, are being recruited from 13 community-based organizations, clinics, drop-in centers, and shelters in Los Angeles and New Orleans. Youth are screened based on self-reports and rapid diagnostic tests for HIV, drug use, and sexually transmitted infections (STI) and then triaged into one of three studies: 1) an observational cohort of acutely infected youth receiving intensive ARV treatment (N=36) and a treatment naïve comparison group (N=36); 2) a randomized controlled trial (RCT) for YLH (N=220); or 3) a RCT for YHR (N=1500). Each study contrasts efficacy and costs of three interventions: an automated messaging and weekly monitoring program via text messages; a peer support intervention via social media sites; or coaching, delivered via mobile, in-person, or virtual video contacts. Optimizing the HIV Prevention and Care Continua are the primary outcomes. Repeat assessments are conducted every four months over 24 months to engage, retain, and monitor youth’s status on an ongoing basis.

**Discussion:** These studies evaluate if HIV can be stopped when services are tailored to communities’ risks/resources; YLH and YHR are concurrently addressed; interventions are implemented with a novel approach to defining “evidence-based”; mobile technologies are leveraged, with in-person contacts being reserved for the youth most resistant; and a Stepped Care approach is adopted in delivering interventions, starting with the least intensive
intervention and stepping up intensity until the desired outcome is achieved.

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**Key Words:** HIV/AIDS, homelessness, LGBTQ, gay, bisexual and transgendered youth
Introduction

America's HIV epidemic among youth aged 12-24 years old has more than doubled in the last 15 years [1]. Despite dramatic improvements in the biomedical treatments for both preventing and treating HIV infection [2-4], American adolescents are increasingly likely to become infected, are not learning they are HIV seropositive when they have become infected, and are not using antiretrovirals (ARV) for prevention or care. ARV use among individuals living with HIV reduces the risk of transmitting HIV by up to 96%, a strategy known as Treatment as Prevention [2]. Additionally, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) – preventative strategies that involve taking ARV medications before or immediately after potential HIV exposure, respectively – have been shown to be effective in preventing HIV infection among at-risk individuals when used correctly [3,4]. However, we are failing to reach both youth living with HIV (YLH) and high risk seronegative youth (YHR) to engage them in ARV-related interventions. To stop HIV infection among adolescents, we need innovative intervention strategies, broadly implemented, that are consistent with the following principles:

1) HIV prevention and care must be planned, tailored, and executed at a local level;
2) The strategies to prevent acquisition of HIV are increasingly similar to those to treat HIV; similar strategies can be successful with youth of different serostatus;
3) Syntheses of evidence-based HIV intervention programs developed over the last 30 years provide models and practices that can be utilized in today's interventions, even when novel technological communication modalities are now broadly available;
4) Mobile technologies are an efficient strategy for diffusing information, messages, engaging youth, and enhancing self-monitoring, regardless of the specific platform utilized;
5) Interventions must be the least intensive needed to result in behavior change for any individual youth and, therefore, more cost-effective for populations than designing to meet the needs of youth – a Stepped Care approach may be more useful than standardizing intervention packages; and
6) Our scientific breakthroughs are only relevant if we can recruit, retain, and keep engaged lifelong YLH and YHR.

This paper describes the strategy underlying a set of studies being mounted to see if we can increase youth’s uptake, maintenance, and retention in the HIV Prevention and Care Continua. Acutely infected YLH, YLH with established HIV infection, and YHR are being enrolled in three, inter-related studies – an observational cohort, and two randomized controlled trials (RCT). This article summarizes the rationale behind these studies, including the recruitment, retention, assessment, and intervention strategies common to three, interrelated, longitudinal HIV prevention and care studies designed on the basis of the principles outlined above. Individual protocol papers in this volume outline each specific trial [5-7]. The integrated data analytic protocols [8] and strategies for monitoring sexually transmitted infections (STI) across the studies [9] are concurrently available in this issue.

Nationally, there is great similarity in the adolescent HIV-affected subgroups, yet the optimal plan to “Getting to Zero” [10] requires individual community tailoring. Gay, bisexual, and transgendered youth (GBTY) in large urban inner cities are also those most likely to be YLH, especially Black and Latino GBTY [11]. In addition, young people with mental health and substance abuse disorders, those who experience homelessness and sexual abuse, or those with histories of incarceration are at increased risk for acquiring HIV [12-15]. These subgroups are, again, over-represented among Black and Latino, low-income youth. YLH in the United States are concentrated in the South and along the West and East Coasts, with the majority of YLH in all regions living in urban areas [11]. Therefore, we selected Los Angeles (LA) and New Orleans – two diverse HIV epicenters – to carry out the three studies.

Policy makers will be challenged by the scale of LA to find and engage YHR and YLH among the 10.1 million persons and across 4750 square miles. Fortunately, LA’s HIV epidemic and HIV-related services are concentrated in six major communities within LA County. For example, there are nine youth-serving agencies within 1.5 miles in the Hollywood area of LA.
However, it may take 2 to 3 hours to reach these agencies from different parts of LA. While New Orleans has fewer agencies than LA, the city has a better public transportation system and is much smaller at 350 square miles and with a population of about 350,000 persons. The HIV epidemic in LA is about 86% men-who-have-sex-with-men (MSM) in LA, while in New Orleans 25% of YLH are young women. Thus, intervention efforts must be tailored to both the geography, the cultural norms, and the local HIV epidemic. By designing and testing interventions in these communities, we aim to demonstrate that the strategies and principles are the same, even if tailored to substantially different settings.

The intervention strategies for YLH and YHR are increasingly similar. Rather than creating separate programs, tailoring for serostatus with common intervention modalities is important. ARV have now been demonstrated effective for both: 1) achieving viral suppression among YLH, as well as increasing the quality and length of life; and 2) reducing acquisition of HIV among seronegative persons, i.e., the success of Treatment as Prevention [2]. These breakthroughs have shifted the loci of almost all prevention and care from community to medical settings. This shift has two major implications for HIV prevention for youth.

First, the HIV Prevention Continuum and the HIV Treatment Continuum are similar in the tasks which are required for youth, as shown on Figure 1. Whether a young person is a YLH or a YHR, both must be linked to medical care, have insurance to cover payments for medical care, and have the transportation and skills to navigate a medical system. In addition, optimal care for both YLH and YHR is to prescribe ARV, again, resulting in the need for both to adhere to medical regimens over time, have regular check-ups, and anticipate when their medications need refills. YLH and YHR must both be monitored for issues like side effects and toxicities over time. Both are likely to experience stress and, potentially, mental health symptoms associated with the enhanced burdens of living with HIV or adhering to health regimens not shared by peers. Because such a high percentage of YLH and YHR are GBTY, coping with stigma from others towards their sexual orientation and coming out to others, or disclosing
either their sexual orientation or status, is similar across serostatus [16]. These similarities suggest that the interventions for these youth can be fundamentally similar.

**Figure 1.** Similarity of the HIV Prevention Continua for seronegative youth at high risk for HIV (YHR) and HIV Treatment Continua for youth living with HIV (YLH).

Second, the medicalization of HIV is likely to be a central issue in youth not being reached by HIV services. In the United States, Black and Latino adolescents are less likely to utilize medical care than peers of other ethnicities [17]. Furthermore, providers are uncomfortable bringing up sexuality; 40% have difficulty bringing up the human papillomavirus (HPV) vaccine, even with parents [18]. As we described above, YLH and YHR are likely to be the most marginalized of adolescents. Homeless, substance abusing, mentally ill, impoverished, GBTY ejected because of their identity (43% of GBTY) [19] are not the youth who are seeking medical care. These youth are more worried about where they will get their next meal than an illness which may kill them in 15 years. Street outreach programs, shelters, bars, hook-up settings, or social media sites associated with risk behaviors (e.g., GRINDR) are the most likely places to access these youth. Therefore, interventions for YLH and YHR are likely to need community recruitment strategies. The projects described in this article adopted recruitment approaches that were predominantly community-based, in addition to being located at adolescent medicine sites.

Replication of evidence-based interventions (EBI) with fidelity, today's scientific standard for defining EBI [20], is unlikely to occur. We need alternative strategies to leverage the
scientific contributions of the last 35 years of HIV prevention and treatment research. The Centers for Disease Control and Prevention (CDC) has identified over one hundred EBI for YLH and YHR and trains about 3,000 HIV providers each year in EBI [21]. However, fewer than 50% of trained providers ever attempt to implement the EBI [22,23] and fewer than 20% of those providers ever implement the EBI with fidelity [22]. High engagement typically requires personalizing a strength-based approach, setting clear expectations, and having consistency in the persons who interact with the youth so that a strong relationship with one person is established [24,25]. Adhering to a manual is likely to stop such personalization.

Our team has rated manuals of adolescent HIV interventions and found that each EBI shared common components, principles, and skills [26-28] and has experimented repeatedly with allowing more flexibility among community providers in the delivery of EBI. We have used an alternative training modality in three successful RCT, each with a different delivery method [29-33]. Instead of replicating a manual with fidelity, coaches are trained in the foundational theory of behavior change (people change slowly, over time, with small steps, in relationships, with opportunities and rewards), the shared principles of behavior change (e.g., Be Prepared; Act on facts, not feelings); and 11 skills shared by 80% of all child and adolescent EBI [34,35]. Those skills are repeatedly practiced with all interventionists, tailored to the topic areas relevant for HIV [36-41].

The intervention strategies used for both YLH and YHR in this set of studies build on the common features of existing HIV EBI [42,26,27]. However, rather than name a new program and hope that CDC will diffuse it widely or having researchers try to sell their program to others in a marketplace, we encourage and want to provide a model to the scientific field that is disruptive to current standards of evidence [43].

Ratings of manuals of adolescent HIV interventions have demonstrated that all HIV EBI:

- frame an issue (e.g., PrEP is a like a daily vitamin; take medication to live a long and healthy life with HIV, you are not dying);
• communicate knowledge regarding HIV (e.g., PrEP can stop HIV acquisition), but each informational message must be transformed into an action in youth’s daily routines;
• remove barriers to reaching a youth’s goals; and
• build social support to sustain healthy behaviors.

With this set of tasks, the key messages for YLH and YHR are similar. Interventions for both YLH and YHR need to address medical care linkage, medication access, consistent utilization, routine monitoring, and sexual and substance use behaviors. Not having scripted, sequenced manualized content, however, allows personalization of HIV programs to the profile and histories of individual youth.

There are three intervention approaches which will be explored in this proposal, based on this model: two are embedded in mobile technology approaches. Our technological approaches are described below. Coaching, the third intervention modality, is the intervention strategy most reflective of adopting the common components, processes, and theoretical model of EBI. Over the past decade, there has been a dramatic increase in popular interest and scientific literature on individual coaching [44-46]. This team has utilized coaching as the intervention approach in three RCT in South Africa and Los Angeles with mothers and children [47,32,33]. We also mounted a UCLA Family Commons, a wellness center in a shopping mall, based on coaching models. From these experiences, we have a set of practice guides available to use in training the coaches in this intervention – designed for coaches with relatively little education or professional experience.

Technology provides an opportunity to intervene, scale, broadly diffuse, and monitor YLH and YHR to enhance HIV prevention and treatment in a cost-effective fashion. Almost all adolescents (92%) go online daily, with mobile devices being a primary driver of teen internet use [60]. Rates of mobile phone, smartphone, and internet usage increase with age, and nearly 90% of young adolescents (age 13-17) have a mobile phone [48]. Texting is particularly important for adolescents; 90% of those with phones text, typically receiving and sending 30
texts each day. Similarly, over 90% of adolescents under age 18 go online daily, more than half several times a day. Smart phones are increasingly available among youth, including Black and Latino youth, decreasing the digital divide which reflected higher access to technology by White and middle class youth, compared to peers of other ethnicities. In fact, African-American and Latino youth have higher rates of smartphone and internet use than White youth [48]. Ownership, access, and use rates are similar for homeless youth [49]. Much of this online activity is driven by social media, particularly via smartphones, with over 70% of adolescents under 18, for example, using Facebook and other applications (about half also use Instagram and Snapchat) [48].

The interventions proposed in this study will use text-messaging and social media to engage “youth where they’re at” in the digital environment as preferences and functions change. Importantly, mobile phones continue to receive text-messages even when data plans run out of credit to use apps’ and mobile-web browsers or send text-messages. Therefore, the core component our technology strategy will be the Automated Messaging and Monitoring Intervention (AMMI), a text-message-based program that all youth in the three studies will receive. Reviews of text interventions have found that text messages increase ARV adherence [50] as well as adherence to other chronic disease medical regimens [51]. Text messages are efficacious to change both the health-seeking and adherence behaviors of YLH and to reduce sexual and drug-use behaviors of high-risk youth [52,53]. Texts are excellent vehicles for promoting health and connecting adolescents to the healthcare system. Features of text messaging are clear: weekly is better than daily, follow-up phone calls are needed if no response to a weekly text, and direct step-by-step instructions are better than vague support [54]. Yet, while we are using text messaging, texting is a specific delivery modality.

Social media is also a strategy being used by coaches and to engage and to support their youth. Mobile and social media technology-based engagement, retention, prevention, and
mobilization strategies are likely to be scalable [55,56]. This study will test whether they are also efficacious and cost-effective in shaping healthy, HIV-related routines among youth. The design and selection of our delivery format is flexible and will be adapted over the five year grant period to be the modalities that are currently highly utilized. The selection of our delivery modalities is always in service of the functions not the format specific mobile communication format. Across each study, automated messaging systems aim to saturate youth’s lives with HIV-related messages, support youth to acquire self-monitoring skills, and emotionally encourage youth, providing support. The specific modality used to accomplishing a function is not critical.

A Stepped Care approach is likely to reduce training, implementation, and costs of delivering interventions for YLH and YHR. Manualized interventions of EBI provide the same dose, scripts, and content for all persons in the targeted population – this is likely to overserve the needs of many youth. A disruptive approach [57,43] calls for the least intensive approach to be implemented that results in the desired behavior change. The Stepped Care model is a cost-effective and patient-centered approach to improve treatment outcomes for chronic illnesses [58]. This model starts with the least resource-intensive interventions first, and steps up the intensity of the intervention only as needed to reach the desired outcome [59]. Given its clinical and financial benefits, the Stepped Care model has been used widely in the management of mental health problems, diabetes, and obesity [60,61]. Stepped Care might also be an efficient method of delivering successively more intensive interventions to YLH or YHR. Although the designs of the two RCT testing interventions which vary substantially in intensity differ (AMMI, peer support on social media, or coaching), together these studies provide a model of starting with less intensive interventions and increasing the intensity if the targeted outcome is not achieved. Rather than everyone getting the same intervention, the dose and type of intervention is linked to outcomes. In the RCT with YHR, the youth are randomized to different modalities – AMMI, social media, coaching, or a combination of these strategies. The modalities,
themselves, vary in the cost and intensity of delivery. Within the context of each modality, however, youth engagement and responsiveness to the intervention varies substantially.

YLH and YHR need long-term engagement and repeat monitoring of their health status to reap the benefits of our scientific breakthroughs. The success PrEP as a biomedical prevention strategy and ARV for treatment [2,3] demonstrates the potential of biomedical prevention. Our experience with adolescents demonstrates that this potential is yet unrealized. In each of the landmark HIV studies with adults, each of which had a behavioral intervention, adherence appears to be around 50% (although the exact percentage was difficult to determine, as the article was vague) [62]. Youth are typically characterized as less adherent than adults [63], especially when long-term adherence is required. The HIV Prevention Continuum [64] requires a prevention toolbox that includes repeat HIV and STI testing, PrEP, PEP, condoms, and risk-reduction strategies for seronegative youth. The CDC recommends monitoring quarterly for YHR. Similarly, YLH must also have their viral load tested repeatedly, be monitored for concurrent STI, drug use, and other factors which will impact adherence, as well as for potential ARV-related toxicities. Ongoing counseling, support, and outreach is likely to be required over time for YLH and YHR, given the requirements of optimal prevention and treatment. Thus, we are identifying a cohort of the GBTY and YHR at highest risk for HIV, linking them to medical care and to intervention studies, and testing them repeatedly for HIV and STIs at four month intervals. This cohort will be recruited and maintained over time by a centralized team in both LA and New Orleans. In summary, this is a program project which has three interrelated studies. These studies also share a common assessment, retention strategies, and ongoing monitoring of HIV outcomes, substance use, STI, mental health, and sexual risk behaviors. The recruitment and retention studies aim to operationalize the best practices outlined by the CDC for those infected and at risk of acquiring HIV. The one deviation from CDC is that we plan three annual assessments, not four (due to costs).

Methods
Each individual study and the overall design was approved by review boards of the Adolescent Medicine Trials Network (ATN) and the University of California, Los Angeles (UCLA), with UCLA serving as the ethical review body for investigators from collaborating universities (IRB#16-001372).

Organizational Structure

The Comprehensive Adolescent Research and Engagement Studies (CARES) operate within an organizational system that is designed to bring multiple, interdisciplinary perspectives to every aspect of a set of collaborative studies. A Management Core provides leadership and ensures the excellence and consistency of study procedures to maximize steps along both the HIV Prevention and Care Continua. For example, experts in behavioral and clinical adolescent medicine, community interventions, and pathogenesis of HIV infection ensure successful recruitment and engagement of participants, best practices for handling laboratory samples consistent with scientific standards, and excellent medical care for both seronegative and seropositive youth. This leadership team has collaboratively created and reviewed all protocols and functions as internal peer reviewers.

The Management Core also coordinates and manages the IRB for each study, monitors and reports adverse events, convenes Advisory Boards, and works across studies to ensure all activities are consistent with the ATN and National Institutes of Health (NIH) policies and procedures. Internally, monthly cross-team conference calls review quality assurance data to maintain progress in all aspects of the studies. Monthly peer review seminars encourage the development of new ideas and proposals to improve the CARES study, and the External Scientific Advisory Board will also be consulted on the evaluation of these new protocols and ideas prior implementation.

Parallel to its responsibilities for ensuring excellent protocols and procedures for each team, the Management Core contains the city-based Recruitment, Engagement, and Retention Center (RERC) teams. Securing the cohorts of YLH and YHR required for our three studies
requires substantial experience and implementation skills. Each of the city-leaders has the administrative and implementation experience, as well as on-the-ground relationships with community-based organizations, to be able to screen up to 2,250 GBTY and YHR per city over 24 months, secure and maintain cohorts of 220 YLH and 1,500 YHR over 24 months, and maintain a cohort of 72 HIV acutely infected youth or treatment naïve YLH. RERC teams in New Orleans and Los Angeles face many shared and some unique challenges. Weekly cross-team calls allow them to test, evaluate, and share solutions to emerging problems in the field. The efforts of the RERC teams shape the ability of all studies to achieve their goals. All recruitment is centralized in these teams, as is the longitudinal follow-up.

Finally, the Management Core leadership and the RERC teams interact with the Public Health and AIDS offices in each city, updating and getting recommendations on an ongoing basis to ensure that CARES programs will be diffusible, if efficacious in this trial. Figure 2 shows the relationship between the Management Core, which coordinates the three studies.

**Figure 2.** Organizational relationships between Management Core and the four other study teams, as well as the advisory board of this program project.
Study Design

A set of three, inter-related studies aim to address five themes identified as a high priority by the Office of AIDS Research at the NIH in the United States [65].

**ATN Protocol 147: Acute infection among adolescents.** A cohort of acutely infected YLH will be aggressively treated with medications that are the current standard in the field and repeatedly assessed at four month intervals to examine if the opportunities exist to keep viral reservoirs low, which should slow disease progression over time (Nielsen and Bryson, Principal Investigators). The immunological and viral reservoirs of acutely infected YLH will be compared to treatment-naïve YLH.

**ATN Protocol 148: A Stepped Care model for YLH with established HIV infection.** Adapted from the chronic disease literature, this study will identify whether a Stepped Care approach is better than a Standard Care approach to identify the minimum level of intervention needed to achieve viral suppression among YLH in a RCT design. There are three levels of the
Stepped Care Intervention: 1) AMMI, 2) AMMI and peer support via social media; and 3) AMMI, peer support, and coaching. Figure 3 outlines the study design and Table 1 lists the conditions in the Stepped Care condition.

**Figure 3.** Design of the randomized controlled trial for youth living with HIV (YLH).

**Table 1.** Outline of the components in the Stepped Care Condition for youth living with HIV (YLH).
### ATN Protocol 149: Engaging seronegative youth in the HIV Prevention Continuum:

staying engaged in medical care, adopting PEP after HIV exposure or PrEP prior to HIV exposure, or a behavioral protection strategy, as well as repeatedly testing for HIV on an ongoing basis every four months. There are four active treatment conditions, as summarized on Figure 4. The conditions are: 1) AMMI alone, 2) AMMI and peer support via social media; 3) AMMI and coaching; or 4) AMMI, peer support, and coaching.

**Figure 4.** Design of the randomized controlled trial for youth at highest risk (YHR) of HIV.
Recruitment into Studies

**Interviewers.** A single RERC team operates across cities, with separate supervisors in each city. A minimum of 10 interviewers, reflective of the gender, sexual orientation, ethnicity, and life experiences of our target population of YLH and YHR are certified as HIV test counselors and trained for 4-6 weeks on the following:

- Phlebotomy and blood protocols
- RDT (Alere™, Xpert®)
- Coping with adolescents on drugs
- Suicide and crisis management
• Interview skills and role playing
• HIV 101
• Study protocol
• Tracking and follow-up
• Legal and ethical mandates (i.e. mandated reporting of HIV and other STIs)
• Cultural competency (LGBTQ and transgender-specific training)
• Cyber bulling
• Housing issues

All contacts are documented in real time on tablets; supervisors review these data reports weekly. There are monthly in-service trainings and random field visits to ensure high quality work.

Sites. In each city, there are collaborating agencies whose staff implement the study protocols, as well as sites at which we place our interviewers. These sites change over time based on the youth population and time of the year. The following sites are the Los Angeles sites:

• Los Angeles LGBT Center – a leader in serving GBTY nationally with health, social services and housing, culture and education, leadership and advocacy programs.
• Covenant House California – a non-profit agency that serves at-risk homeless youth living on the streets between the ages of 18 to 24 years. Covenant House LA team provides a full continuum of services for youth, including healthcare services, substance abuse counseling, mental health and behavioral health treatment, case management, educational services, food, clothing, employment training, and long-term, transitional living, among several other services.
• The Village Family Services – serves primarily Latino children and families victimized by violence, abuse and neglect in order to improve the wellness of at-risk foster and homeless youth ages 12-25 years. Its location, in the Valley area of LA, leads it to serve a large GBTY population.
• Safe Place for Youth (SPY) – is a homeless drop-in center located in Venice, CA.
• Transition Age Youth (TAY) Academy – helps young adults ages 18-25 years, who are experiencing emotional, behavioral and mental health difficulties. Many of the TAY students have aged out of foster care, have not completed their education, have limited prospects for finding a job and need support to avoid or overcome drug and alcohol misuse.

• The Long Beach Gay and Lesbian Center – provides health care, advocacy, mental health, and referral services to youth, especially YLH and YHR who are GBTY.

• Miller Children’s Hospital – provides services for YLH in the Long Beach area of LA.

• The Riverside County Regional Medical Center, the San Bernardino Public Health Clinic, Borrego Health Clinic, Eisenhower Medical Center, and True Revolution are agencies serving GBTY in an area about 50 miles east of downtown LA. This area has a relatively high percentage of networks of substance abusing persons and GBTY in an underserved and semi-rural section of the greater LA area.

The New Orleans Recruitment Sites are:

• Tulane Adolescent Drop-In Center – provides a welcoming and safe space for street youth, ages 13-25 years, which offers case management, housing and housing support services, behavioral health counseling, life-skills groups, and employment support.

• Tulane Adolescent Drop-In Clinic at Covenant House – provides comprehensive primary healthcare including behavioral, transgender and reproductive health care to youth 13-24 years old from all racial/ethnic groups.

• Tulane T-Cell Clinic – houses several clinics including ACCESS Health, a Federally Qualified Health Center. ACCESS Health provides general medical services across the age span and the T-Cell clinic serves children, youth and adults living with HIV.

• University Medical Center Infectious Disease Clinic – provides services primarily to
people living with HIV and provides free care to people who do not have medical insurance. Clinic services include provision of primary HIV medical care, specialty care tailored to people living with HIV, case management, mental health, nutritional services, transportation, and dentistry.

- Crescent Care (formerly NO/AIDS Task Force) – provides social, medical, mental health, and material support to people living with HIV and GBTY.
- Brotherhood, Inc. – provides HIV/STI testing and linkage to HIV prevention and care, prevention curricula.
- Social Media Recruitment – Recruiters use Instagram, Snapchat, and Facebook to create interest and visibility for the study. Recruiters post pictures and send messages via social media in real-time while at recruitment events to encourage youth to approach the recruiters.

Participants. At each of these sites, either agency staff or UCLA/Tulane staff approach youth to participate in the CARES. Recruitment approaches are scheduled to stagger across the days of the week and time of the day to ensure all youth receive an approach for participation. Youth must be either YLH, transgender, a GBTY with at least one additional risk factor for HIV, or a youth with three risk factors for HIV (homeless, hospitalized for a mental illness in their lifetime, spent time in jail, Black or Latino, or having a partner who is a person living with HIV, unprotected anal sex in the last 12 months). Youth who meet the criteria are then asked to voluntarily participate with informed consent in a study and complete a baseline interview.

After obtaining voluntary consent, youth are screened for study eligibility with a 16-item questionnaire conducted by the interviewer and receive a rapid point-of-care fourth generation Alere™ test (Alere, Waltham, Massachusetts) for HIV infection, RDT for STI, and RDT for illicit drug use and current alcohol use. The STI testing includes testing for Neisseria gonorrhea (NG).
and Chlamydia trachomatis (CT) using the FDA-approved Xpert® CT/NG assay (Cepheid, Sunnyvale, California). The Xpert® CT/NG assay provides test results in 90 minutes. Our team has validated the Xpert® CT/NG system for vaginal and extra-genital CT/NG infections using self-collected swabs. The Xpert® CT/NG is an instrument ranging in size from a single device about the size of a small coffee maker to 4 and 16 unit devices that sit on a desk top. Test results are automatically downloaded into an attached secure and encrypted laptop, which interviewers can check to communicate results with participants directly. Persons with positive NG and CT test will be offered same-day treatment and expedited-partner therapy in accordance with CDC recommendations. Screening for syphilis infection occurs using the CLIA-waived rapid point-of-care fingerstick whole blood treponemal antibody test Syphilis Health Check™ (Diagnostics Direct, Stone Harbor, New Jersey). Syphilis is particularly important, given the high rates in New Orleans. Persons with reactive rapid syphilis tests have their venous serum tested for rapid plasma reagin (RPR) and T. pallidum particle agglutination (TP-PA) determination. Those with active syphilis infection will undergo syphilis treatment according to CDC recommendations (single dose benzathine penicillin 2.4 MU for early infection and 3 doses weekly for late or unknown duration infection). Dr. Klausner provides training and oversight to all sites and staff in the diagnosis and management of STIs and review each case of syphilis to assure proper management. See Shannon et al, this volume for a more detailed description.

All interviewers have been trained and are implementing Direct Observation Treatment for CT and NG. See Protocol by Shannon et al. in this volume for a longer description.

Table 2 summarizes the content areas covered in the baseline interview. These interviews are highly similar across studies with only small variations regarding past ARV experience and adherence for YLH, PrEP reception, knowledge, and experience for YHR, and probes regarding stigma and coming-out for GBTY.
Table 2. Domains repeatedly assessed every 4 months throughout the 24 month follow-up period for all participants in every study.

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<thead>
<tr>
<th>Rapid Diagnostic Tests for HIV, STI &amp; serious drug use*</th>
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<tr>
<td>Current health provider?</td>
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<td>Current access to provider?</td>
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<td>Current medical appointments?</td>
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<td>Current ARV prescription?</td>
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<td>Relationship with provider?</td>
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<td>Where ARV prescription?</td>
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<td>Drug? Dose?</td>
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<td>Pharmacy?</td>
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<td>Need new drug access card?</td>
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<td>ARV Adherence?</td>
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<td>Physical health?</td>
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<td>Comorbidities?</td>
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<td>Homelessness?</td>
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<td>Mental health symptoms, care &amp; hospitalization?</td>
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<td>Drug use?</td>
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<td>Alcohol use/abuse?</td>
</tr>
<tr>
<td>Illness? Hospitalization?</td>
</tr>
<tr>
<td>Gang involvement?</td>
</tr>
<tr>
<td>Criminal justice contact?</td>
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<tr>
<td>Sexual partners? Condom use?</td>
</tr>
<tr>
<td>Social support?</td>
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<tr>
<td>Employment? School?</td>
</tr>
<tr>
<td>Income?</td>
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<tr>
<td>Pleasant activities?</td>
</tr>
</tbody>
</table>

*Youth Living with HIV with not be retested for HIV.

Youth meeting the eligibility criteria are then triaged to one of the three studies based on the results of an initial HIV test. Seronegative YHR enter Protocol 149. YLH enroll in Protocol 148 if they have had ARV previously and are non-virally suppressed. Protocol 147 enrolls all youth with acute HIV infection and treatment naïve YLH with established HIV infection, until a
critical threshold of 36 acutely infected YLH are recruited. After an additional 36 treatment-naïve YLH are recruited, all YLH who are not virally suppressed are triaged to Protocol 148 for YLH. Among the 1500 YHR in Protocol 149, we anticipate there will be acute infections over time and, when occurring, these youth will be triaged to the study of acute infection. Figure 5 diagrams the flow of participants in the study. YLH must be non-virally suppressed in order to be eligible as a participant for ATN Protocol 148. Because previous research has found YLH to be inconsistently suppressed over time [66], we are currently enrolling virally suppressed YLH in an observational cohort. If these YLH become non-suppressed, we will then enroll them in ATN Protocol 148.

**Figure 5.** Flow into the three integrated studies in the CARES Program Project.

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*Intervention*
Specific details of the interventions utilized in each study are available in individual protocol papers [5-7]. Because the challenges are so similar, the AMMI, the peer support, and the coaches are shared across the studies. Please note that the design of ATN Protocol 148 is a true Stepped Care approach; only if a YLH is not virally suppressed at a four-month follow-up does the next level of intervention become triggered. However, in ATN Protocol 149, YHR are randomized to different intervention modalities. While a sample size of 220 is sufficient in ATN Protocol 148 to test the efficacy of an intervention, it is necessary to monitor 1500 YHR in order to expect to identify 36 acutely infected YLH.

Coaches are B.A. level persons who also share the cultural, ethnic, gender, sexual orientation, and life experiences of the target population of young people in ATN Protocols 147, 148, and 149. The coaches are trained for 1-3 months, depending on the individual coaches’ skills in the following areas:

- An underlying theoretical model (people change slowly over time, in relationships, with opportunities and rewards);
- The skills common to EBI, with substantial role playing regarding many prevention messages (Rotheram-Fuller et al., 2016);
- HIV education and content, PrEP and ARV efficacy and regimens;
- Establish relationships with local providers with visits and placements;
- Strength-based case management approaches and a strength-based assessment; and
- Emergency procedures for suicidal, homicidal, and seriously disturbed youth.

The training model utilized in ATN Protocols 147, 148, and 149 is summarized on Figure 6. Based on work by Rotheram-Borus and colleagues [34], coaches are not trained to replicate a manual with fidelity. All coaches are taught basic skills common across EBI, a theory of change based on the social cognitive model and a set of basic intervention messages. Because coaches reflect the target population, they use their cultural knowledge to tailor and help youth implement these skills daily.
While the AMMI and peer support interventions are automated and managed by a combination of intervention supervisors and data analysts in real time, the coaches are trained to be able to communicate via text, Instagram, in-person visits, Skype, Zoom, and any other modality preferred by the youth. Coaches have made brief videos of themselves and share these vignettes with the youth on their caseload.

We can anticipate that many YLH and YHR are not linked to health care, especially low income Black and Latino youth. One in three youth with a health problem do not seek or receive care within a year of symptom onset and those who do seek care use adult primary health care (not adolescent medicine clinics) [67,68]. At least 5% of adolescents use emergency departments for all health care received [69]. If youth’s providers are within a Health Medical Organization (HMO), youth are 50% less likely to receive any care (preventive or treatment of disease) [68]. More than 40% of Black and Latino youth have had no health care in the previous year [70]. Most adolescents believe their illnesses will go away (65%) [70]. Adolescents are particularly vulnerable to rejecting medical care due to the poor social skills of their health providers and the disrespect felt by their providers [71]. GBTY are even less likely to receive medical care and appropriate services [72]. About one-third of youth get no preventive health visit between the ages of 12-17 years old [67]. Youth with mental illness are even less likely to
receive services [73] and HIV is linked to serious mental illness [74]. In ATN, fewer than 50% of YLH were linked to care within a year of diagnoses; at 32 months, about 30% were still not linked to care [75]. Thus, linkage to health care is the first challenge that YLH must accomplish, on their trajectory to viral suppression [75]. If not linked to care or uninsured, it is impossible to achieve viral suppression. To overcome the challenge of YLH being linked to care, on intake into the study, each youth is assisted to complete the universal application for access to free or reduced cost ARV through the Ryan White Program. Through patient assistance programs, seven national pharmaceutical companies provide free or low-cost access to ARVs to patients who qualify [76]. We provide each youth with a laminated card for the free ARV access and the website to the free ARV access at recruitment.

Analysis

CommCare (Dimagi, Cambridge, Massachusetts) is an open-source support program utilized by the research team for data collection and monitoring. Automated quality assurance reviews recruitment rate, uptake of testing, HIV/STI results, intervention implementation, and responses to weekly surveys on a weekly basis. All investigators, assessment, and intervention teams review these reports weekly. Reviewing these data as a team, with representatives from each study arm, across all locations, and with input from interviewers, coaches, coordinators, and principal investigators allows for continual iterative improvements in all protocols.

Senior statisticians meet monthly to review data for each protocol. The central team supports additional researchers on projects utilizing the de-identified data from inception to diffusion. A more detailed discussion of the plan to analyze the data is available in a separate article in this issue [8].

In addition, cost-benefit analyses is being performed based on a modified form of the UNAIDS 2010 template [10]. The total costs of each intervention component of each study, as well as the costs of repeatedly assessing a cohort to facilitate engagement are monitored on an ongoing basis. Costs are of two types: 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 the criminal justice system). Intervention costs are obtained from project records and will 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. Staff monitor their time and activity reports one week quarterly via an app to provide accurate estimates of staffing costs. The costs of additional services are derived from respondent reports of utilization, medical records, and are estimated using publicly available data. Research-specific costs (e.g. incentive payments, informed consent, screens, 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. These data inform not only the cost-utility analyses for this study, but also future modeling studies by other researchers.

Resource Sharing Plan

Data and research findings generated from this study will be made available, in accordance with the NIH Data Sharing Policy [77], to all researchers in both the private and public sector. We adhere to the NIH Public Access Policy that requires final, peer-reviewed manuscripts be submitted to the National Library of Medicine’s PubMed Central upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. Study results are to be also made available to researchers, funders, service providers, the target population, and general public.

In addition, after all data are de-identified, cleaned, and validated, and main findings are published, we will make study data available to the scientific community and the general public on the DASH open-source system of the National Institute of Child Health and Human Development. Our data sets will be publicly accessible, available in non-proprietary formats, free of charge, with unlimited use and distribution rights. Data sets will also be made available
to those who make a direct request to the ATN Coordinating Center. No identifiers will be included in these data sets. The names of the sites where data are collected may not be released beyond the immediate study team to further protect the privacy of participants. To adhere to the “open data” quality standards, we will follow Dublin Core International metadata standards [78]. We will ensure data consistency with the five-star open data deployment scheme [79].

Finally, across all the proposed studies, we will make available the intervention training guides, tools, manuals, and materials to other interested organizations and agencies in the United States and on open websites.

Discussion

This innovative set of inter-related studies provides a novel, scalable, and flexible technology-based approach for addressing the HIV epidemic among youth in the United States. Interventions are designed to optimize adherence to the HIV Prevention Continuum among YHR and the HIV Treatment Continuum among YLH using technology-based approaches that emphasizes function over platform and can be tailored to community's risk/resources. Together, the proposed studies will offer counties, cities, and communities a potential system for integrating and coordinating prevention and care for YLH and GBTY and YHR using a comprehensive, flexible approach for which costs and outcomes are known. We expect our results will be broadly applicable to diverse agencies and jurisdictions including NASTAD (National Association of State AIDS Directors), CDC, HRSA, state and local health departments, and heavily impacted communities.

One of the major innovations in this program project is to experiment with acute infection interventions for YLH. This study is led by the Nielsen/Bryson team, a team that has been involved in pediatric HIV research since the late 1980’s. Our acute infection research protocol which is described in detail in the Nielsen et al paper in this volume is based on our team’s successful CURE research with pediatric populations. We are among the first to extend this
cutting-edge biomedical research to adolescents and young adults. One of the biggest challenges we face is identifying a sufficiently large pool (N=36) of youth in the acute infection phase. The systems that we are implementing (e.g. regular HIV/STI testing, weekly automated monitoring of signs and symptoms of HIV infection), if successful, can lay the groundwork for accessing this difficult-to-identify group. Even if we identify biomedical interventions that can reduce the size of the viral reservoir and achieve a functional CURE, clinicians and researchers need a viable, cost-effective approach for identifying and engaging newly infected youth in the acute infection phase. The work we are conducting will advance our knowledge in this important area.

Technology-based integrated approaches offer great promise to combat the HIV epidemic in youth. Information communication technology provides a vehicle through which to intervene, scale, broadly diffuse and monitor YLH and YHR to enhance engagement and progress through the HIV Prevention and Treatment Continua in cost-effective ways. Our team is particularly well positioned to successfully execute this large endeavor having successfully conducted interventions with mobile phones and social media. For more than nine years, we have been collecting data on mobile phones domestically and in resource poor settings (South Africa, Uganda, India), monitoring adherence daily. More importantly, our team has developed guidelines for using mobile and social networking technologies in health research and practice [80]. This experience allowed us to design and test intervention approaches that varied in intensity and were acceptable and familiar to youth using technology that emphasized function rather than platform. Although there is evidence that app-based interventions are efficacious, they are expensive to program, modify, and regularly update, reducing their long-term utility and scalability. Our goal was to be agnostic to the platform, but to focus on the functions we aim to achieve with the mobile platforms, that is to test interventions that could be scalable, adaptable and easily implementable by community-based organizations. Focusing on standardized functions of this platform allows us to evaluate the utility of the approach.
Another contribution of these studies lies in our recognition of the convergence of intervention approaches needed to engage and advance youth through both the Prevention and Treatment Continua. The advent of biomedical prevention approaches has created a bridge in intervention research with YLH and YHR [81]. As described in the protocol papers in this issue, our intervention approaches for both populations are parallel. Both YLH and YHR must be identified, engaged and retained in prevention and treatment services, routinely monitored to achieve the stated outcomes. The work of the RERC is designed to facilitate these activities by continued engagement with youth, routine testing, and monitoring our behavioral and biomedical outcomes. It has been suggested that YHR and YLH may need to have a paraprofessional coach through their riskiest developmental periods (personal communication by Bonnie Stanton, 2016).

Cost and cost-benefits are key aspects of our studies not only for informing policy makers, but by facilitating better estimates in modeling of communities’ combination prevention strategies. Across all types of intervention studies, the costs, benefits, cost-utility and cost-effectiveness are key issues in considering the scalability of each intervention and the value-added per dollar spent on the intervention strategy. A recent modeling experiment on the HIV Prevention Continuum for Men-who-have-Sex-with-Men (MSM) in the United States found that the most successful strategy is to test MSM every three months for HIV infection [82]. However, the approximate cost for repeatedly testing MSM would be $5 billion annually, a prohibitive cost and unlikely to be warranted. It is critical that such modeling exercises are informed by actual data about the costs and yields of interventions for YLH to make informed policy decisions. We are planning to repeatedly test YHR every four months. This frequency of retesting is actually driven by the desire to identify acutely infected YLH. However, this testing will also give us information on the combination of risk factors among youth who go on to seroconvert – telling us who and how to identify YLH. The repeat testing also evaluates one strategy for operationalizing the CDC’s recommended guidelines for identifying YLH [83]. Finally, since no seroprevalence
studies have been conducted among homeless GBTY and YHR in many years, this study will inform public health administrators and policy makers whether to implement routine testing in homeless shelters and gay-identified CBO.

In summary, the United States is challenged to reduce new HIV infections among youth and to broadly implement the preventive interventions (particularly PEP and PrEP) that US scientists have identified. To stop HIV among youth, aggressive programs targeting YHR and YLH must be broadly implemented. This challenge will require modifications of our standard scientific approaches to replication with fidelity of EBI, utilization of new technologies, and practical strategies for engaging and retaining youth in medical care lifelong. The set of studies will examine one set of approaches to achieving this aim.
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Conflicts of Interest

The authors declare no conflicts of interest.
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