Adolescent Medicine Trials Network for HIV/AIDS Interventions
Request for Proposals (RFP)
Research Aimed at the Reduction of New HIV infections in Youth & Research Aimed at the improvement in the Proportions of Youth Achieving Successive Milestones across the HIV Care Continuum

I. Introduction

The US National Institutes of Health (NIH)-sponsored Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) aims to develop and conduct innovative behavioral, community-based, translational, therapeutic, microbicide and vaccine trials in HIV-at-risk and HIV-infected youth ages 12 to 24 years, with a focus on the inclusion of minors. The objectives and overarching goals of the ATN is to increase the numbers of at-risk youth who are aware of their serostatus, and for those who are diagnosed with HIV, to increase the numbers in each segment of the care continuum to 95% and to bend the infection rate curve downward toward zero. Currently, the ATN is comprised of three U19s, each supporting a research program with a well-defined research focus supported by core (e.g. program management, analysis) infrastructures and any needed subject recruitment and enrollment capacity (See Appendix A). Each U19 Program Project will conduct a number of scientifically meritorious research projects and enrollment capacities to permit an effective collaborative effort among the participating investigators. The ATN is further comprised of a U24 Coordinating Center to provide support, coordination, and operational infrastructure to the Network. The ATN's structure allows for the ability to perform high priority studies across the U19s generated from the Network and/or in collaboration with other networks, agencies and other outside investigators.

II. Purpose

The purpose of this RFP is to encourage collaboration among investigators and the ATN by providing funding support for scientifically meritorious research projects that address the research objectives of the ATN in order to augment the research areas of the ATN's U19 Program projects already in progress. This funding opportunity is open to all investigators outside of ATN Principal Investigators whom are currently funded, with the skills, knowledge, and resources necessary to carry out the proposed research, whether or not they are currently affiliated with the ATN. Junior-level investigators paired with appropriate senior mentors are encouraged to apply to this RFP.

III. Background

Greater than ¼ of all new HIV infections in the US occur in youth. These infections are disproportionately distributed among ethnic/racial minorities and men who have sex with men (MSM), with more than ½ of new infections occurring in young African American and Hispanic populations and 72% in young MSM populations. These groups are also unique compared to all others because longitudinal trends of infection over the last decade have increased. CDC guidelines for routine HIV testing across the US have increased the numbers of people identified with undiagnosed HIV infection, however up to 80% of youth are unaware of their infection. Additionally, establishing a durable linkage to care, an activity associated with improved outcomes, remains an elusive goal for many providers. This issue is especially important in vulnerable populations like

youth, who may encounter more obstacles and challenges when attempting to access and stay in care. A significant portion of the youth targeted for the ATN studies will include traditionally difficult to reach populations of medically disenfranchised, low socio-economic status, sexual and gender minority and/or racial/ethnic minority young men and women.

The ATN was established with an infrastructure that includes administrative and managerial support, analytical and data management expertise, subject recruitment and enrollment capacity, as well as scientific and technical expertise to perform high priority studies across the U19s generated from the Network and/or in collaboration with other networks, agencies and other outside investigators. While many important studies have been funded and are currently being implemented by the ATN, mechanisms to rapidly address new or emerging scientific priorities and cross-U19 collaborations were planned as integral components of the Network's establishment. These include a request for proposals (RFP) to identify, develop and implement high quality, innovative and impactful research that will address these priorities utilizing the existing ATN infrastructure. This approach provides the resources and foundation to stimulate novel ideas and study designs from qualified investigators in a timely manner and is most nimble to allow optimal alignment of resources with needs in responding to an evolving youth HIV epidemic.

IV. Funding Source and Mechanism

Up to six awards for two to five years are anticipated. Application budgets are not limited but need to reflect the actual needs of the proposed project. However, if the annual budget is expected to exceed $500,000 in total costs (inclusive of indirect costs) consultation with the ATN and NICHD will be needed. Contact Patrick Sullivan with questions pssulli@emory.edu.

V. Scope of Work

The ATN is interested in receiving proposals for R01-like Research Projects addressing feasibility, uptake and effectiveness of prevention services that include PrEP among youth at risk of HIV infection and in projects to improve linkage, retention and viral suppression outcomes for youth with HIV, especially those with sporadic engagement. Of particular interest are studies that employ innovative designs (e.g. adaptive, comparative effectiveness), target more than one level (e.g. individual and family), adapt methodologies for interventions on subpopulations and youth in different developmental stages, evaluate cost effectiveness and/or leverage collaborations with other Federal agencies (e.g. CDC, HRSA). The study design should be sufficiently described to allow the ATN to determine projected infrastructure requirements [e.g. data management, analysis, subject enrollment needs and venue (e.g. virtual cohort studies conducted electronically)].

The R01-like Research Projects should be planned to be conducted within the United States and leverage existing ATN infrastructure to address an important research area, limited to the following:

A. Develop and examine the feasibility and potential impact of the delivery of novel services, delivery of services in novel settings, and the use of novel engagement strategies for reaching high risk youth and promoting uptake of essential services such as, HIV testing, STI testing, risk screening, condom distribution, PrEP, PEP.

B. What are the best prevention packages, approaches and strategies to promote movement along the PrEP/PEP cascades from awareness to motivation for uptake, to linkage to prescribing providers/systems to uptake, to adherence? What are the determining factors related to discontinuation of PrEP? How do PrEP vs PEP users differ on key factors such as depression, substance users, stigma and risk behaviors?

C. What is the most effective strategy or set of strategies for linking positive youth to care?

D. Test multilevel interventions to promote retention in care and viral suppression among youth who have been linked but not engaged in regular care (or sporadic users)

VI. Proposal Procedure and Requirements

Letter of Intent: Applicant should submit a brief letter of intent that includes the proposed PI's name and institution on letterhead, the names and institutional affiliations of all collaborating investigators, and the research area (specified by letter(s) above) by February 17, 2017 to facilitate the review.

Applicant Package: Applicants are asked to submit a package including the following documents by March 24, 2017:

- Cover Page with the title of the proposed investigation and the names and institutional affiliations of the PI and collaborating investigators
- A completed Concept Sheet in which the proposed investigation is to be described (no more than 10 pages with a minimum font size of 11), including the following:
    - Research Proposal
    - Significance and innovation
    - Additional background and rationale, including information on preliminary studies and/or data pertinent to this application
    - Description of potential ways to integrate with and/or utilize the ATN infrastructure (e.g., scientific cores, scientific expertise; see Appendix A)
    - Human Subjects considerations, if applicable
- NIH biographical sketch for the Principal Investigator and other key personnel
- Budget and budget justification (in PHS 398 forms)
    - Analytical and data management support will be covered separately by the network

  Clearly describe the Research Project, including the project's objectives/aims. Discuss the significance of the work proposed and its scientific contribution to the aforementioned research area(s). The proposal must include a clearly articulated and justified developmental timeline with milestones and contingency plans for anticipated challenges.

VII. Review Process and Prioritization

An independent review committee will review each proposal. The proposal review summaries will then be evaluated by the ATN Executive Committee for prioritization for funding. Specific review criteria will include:

Significance: Does the project address an important problem or a critical barrier to progress in the field? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s): Are the PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Innovation: Does the proposal challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?

Approach: Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Does the project leverage the existing ATN infrastructure such as scientific expertise, cores, or other resources?

Environment: Will the scientific environment in which the work will be done contribute to the probability of success? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements? Will the community be engaged appropriately?

Protections for Human Subjects: For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

VIII. Key Dates/Timeline

RFP Release Date: January 27, 2017
Letter of Intent Due Date: February 17, 2017
Proposal Due Date: March 24, 2017
Review Timeframe: April 2017
Award Issued: After May 1, 2017

IX. Contact Information

Address to which Letters of Intent and proposals should be submitted: ATN U24 at ATNadmin@unc.edu.

Administrative questions may be submitted: ATN U24 at ATNadmin@unc.edu.

Scientific questions may be submitted to: Sonia Lee (Sonia.lee@nih.gov)

APPENDIX A

Brief Descriptions of Currently Funded U19, U24 and Additional Projects

There are several projects already funded through ATN. Descriptions of these projects are provided so that overlap between proposals and what is already in progress is minimized. Keep these projects in mind when developing proposals. In addition, through the U19s there are three cores available, which provide specific assistance to projects and sites. Consider how you may be able to leverage their services in your proposal.

Management Core Descriptions (each U19 is required to have a Management Core):

iTech Management Core:

Management Core provides infrastructure and operational support as well as support communication and collaboration between the research within as well as between the U19s and the ATN Executive Committee (EC). Contact Lisa Hightow-Weidman (Lisa_hightow@med.unc.edu).

Scale It Up Management Core

Management Core includes a Clinical Site Management Center (CMSC) which coordinates activities across 11 adolescent HIV clinics across the United States involved in Scale It Up protocols; and a Recruitment and Enrollment Center (REC) which coordinates protocol/project management, recruitment/retention, and data management for all Scale It Up protocols. The Core also provides coordination and support across and within the U19s. Contact Jeffrey Parsons (jparsons@chestnyc.org).

CARES Management Core

The Management Core is responsible for leadership and networking; communication and problem resolution; administration; and, implementation of the Recruitment, Engagement, and Retention Centers (RERC) in Los Angeles and New Orleans that will identify, recruit and retain all participants and samples for the CARES studies. The Management Core establishes the goals, timelines, monitors deliverables, sets strategies for quality improvement over time, training, and coordination of teams over time. Contact Mary Jane Rotheram (mrotheram@mednet.ucla.edu).

Analytic Core Descriptions (each U19 is required to have an Analytic Core):

iTech Analytic Core:

The Analytic Core provides expertise and systems for the conduct and analysis of qualitative studies, pilot intervention studies, randomized controlled trials (RCTs) and economic studies. The analytic core works with the technology and management cores to set up systems to manage participant recruitment and retention and ensure data quality and security. Contact Eli Rosenberg (Erose2@emory.edu) or Kate Muessig (Kate_muessig@med.unc.edu).

Scale It Up Analytic Core

Our Analytic Core coordinates all quantitative analyses (formative research and RCT analyses) for Scale It Up protocols, as well as analyses of EMR data provided by our 11 clinical sites in order to address HIV care cascade monitoring. In addition, the Core implements and carries out cost effectiveness data collection and analysis for all our protocols, and provides training and mentorship to junior investigators around analytic techniques and approaches. Contact Jeffrey Parsons (jparsons@chestnyc.org).

CARES Analytic Core

The Analytic Core provides methodological and statistical support across the CARES studies from inception to completion, including study design development, data collection, and analysis. The Analytic Core provides a range of technological, biomedical, and behavioral research expertise including fitting complex multilevel models (MLM) to

HIV data with both behavioral and biomarker outcomes, implementation science and cost-effectiveness. The Analytic Core will also be responsible data management, monitoring, security and dissemination. The Analytic Core has expertise in cost effectiveness and cost-utility analyses, as well as substantial experience with interventions mounted on social media sites, and using mobile and computerized interventions. A robust platform has been used in multiple countries with complex time-location stamped interventions is utilized by this core to ensure high quality and real-time assessments providers' behaviors over time. Contact Mary Jane Rotheram (mrotheram@mednet.ucla.edu).

Additional Cores:

iTech Technology Core:

The Technology Core provides services for technology related fields, including mobile technologies, web-based platforms, laboratory platforms, online recruitment and technology-related ethics issues. The Technology Core will serves as a service center, to which individual investigators or site PIs can request specialized assistance or request to use shared resources. Contact Lisa Hightow-Weidman (Lisa_hightow@med.unc.edu) or Patrick Sullivan (Patrick.sullivan@emory.edu).

Scale It Up Implementation Science Core

The Implementation Science Core supports our protocols with core qualitative and quantitative measures of fidelity and intervention fit, and monitors adaptations during implementation. They develop and provide standardized facilitator training, and develop strategies for dissemination of effective interventions. In addition, the Core oversees qualitative data collection and analyses for the Scale It Up U19. Contact Jeffrey Parsons (jparsons@chestnyc.org).

Funded U19 Projects:

iTech

Get Connected:

Online brief intervention that employs individual and systems-level tailoring technology to reduce barriers to HIV prevention care (e.g., HIV/STI testing, PrEP) for YMSM. Primary outcomes for efficacy trial include (1) use of HIV prevention services (HIV testing, STI testing) and PrEP awareness and willingness. Secondary outcomes include PrEP use, sexual risk behaviors, and the linkage and retention in care among newly diagnosed HIV+ cases. Contact Jose Bauermeister (bjose@nursing.upenn.edu) or Rob Stephenson (rbsteph@umich.edu).

YouTHrive:

Efficacy trial of an extended (5-month intervention period) and enhanced (tailored informational content; multidimensional self-monitoring; and gamification components, such as leveling and badges) intervention which leverages peer-to-peer interaction, ART adherence reminders and self-monitoring, and ART and HIV informational content to improve ART adherence among HIV-positive youth of all genders. The primary endpoint is viral load (VL) post-intervention among the full sample (intervention vs. control) and comparing substance-using to non-substance using youth in the YouTHrive intervention. Secondary analyses include durable VL, self-reported adherence, and the associations between intervention components and VL. Contact Keith Horvath (horva018@umn.edu) or Rivet Amico (ramico@umich.edu).

P^3:

P^3 is an interactive smartphone app for HIV-uninfected young MSM and trans women who have sex with men that utilizes social networking and game-based mechanics as well as a comprehensive understanding of what constitutes "best practices" in app development to improve PrEP adherence and persistence in PrEP care. The project will include a study arm (P^3+) that includes P^3 and adherence counseling delivered by a counselor through the P^3 app. We will test the efficacy of P^3 and P^3+ versus a standard of care arm receiving routine PrEP support as recommended in the CDC guidelines to improve PrEP adherence and persistence in PrEP-related preventative care. A cost comparison between P^3 and P^3+ will be conducted. Contact Lisa Hightow-Weidman (Lisa_hightow@med.unc.edu) or Sara LeGrand (Sara.legrand@Duke.edu).

LYNX:

This project will develop a new app, LYNX, for increasing uptake of HIV testing and PrEP. This app will leverage an existing mobile app platform, which will be refined to maximize acceptability among YMSM. The project will then evaluate the acceptability and feasibility of this integrated app in a pilot randomized controlled trial (RCT) among YMSM at risk for HIV acquisition in the US. Contact Albert Liu (Albert.liu@sfdph.org) or Hyman Scott (Hyman.scott@sfdph.org).

My Choices:

This project will use theater testing and an open technical pilot to refine a mobile app, MyChoices—previously adapted from an app tested in adult MSM and guided by the Social Cognitive Theory—to increase HIV testing and PrEP uptake by YMSM. The project will then evaluate the acceptability and feasibility of this integrated app in a pilot randomized controlled trial (RCT) among YMSM at risk for HIV acquisition in the US. Contact Kenneth Mayer (kmayer@fenwayhealth.org) or Katie Biello (Katie_biello@brown.edu).

Compare:

Two distinct mobile apps, LYNX and MyChoices, designed to increase HIV testing and PrEP uptake among YMSM, were developed based on different theories of behavior change, and therefore contain different components, different messaging strategies and different approaches for engaging youth. These apps will be tested in this follow-on research study to evaluate their efficacy. Comparing the apps will allow us to identify any efficacy differences in increasing HIV testing or PrEP uptake between the two apps. If justified, we will combine the components of each app that have the greatest impact on behaviors into a final, composite app for dissemination. Contact Albert Liu (Albert.liu@sfdph.org) or Katie Biello (Katie_biello@brown.edu).

Scale It Up

Tailored Motivational Interviewing (TMI):

The project will test a multifaceted *Tailored Motivational Interviewing Implementation intervention* (TMI), to train adolescent HIV-care clinics on MI, using the dynamic adaptation process to scale up an evidence-based program while balancing flexibility and fidelity. The dynamic adaptation process guides tailoring of MI training at the exploration, preparation, implementation, and sustainment phases of scale-up. Pilot work to develop TMI included tailoring initial workshop training based on innovative methods in communication science, developing efficient fidelity measurement, and preliminary testing of implementation strategies utilizing the dynamic adaptation process. The effect of TMI on fidelity to the original evidence-based program, and secondarily on cascade-related outcomes, will be achieved by using a dynamic waitlist

controlled design with 150 providers nested within 10 of our clinic sites yielding 5 clusters to receive TMI. Contact Sylvie Naar (snaarkin@med.wayne.edu).

Young Men's Health Project (YMHP):

A comparative effectiveness trial of the YMHP intervention (utilizing motivational interviewing and skills building) with two delivery formats (clinic-based versus phone-based) will assess their relative effectiveness in reducing sexual risk and substance use and increasing PrEP uptake among HIV-negative YMSM (ages 15-24), while considering access to health care as a moderating factor. We will conduct the study at three of our clinic sites, with the intervention delivered by trained clinic staff (community health workers). We will collect cost effectiveness data, as well as implementation science data related to feasibility, acceptability, sustainability, and barriers related to implementing YMHP in these settings. Contact Jeffrey Parsons (jparsons@chestnyc.org).

Text Messaging, Cell Phone Support, and Contingency Management (SMART):

Two promising and youth-friendly mHealth approaches have demonstrated significant improvements in adherence among HIV+ youth: cell phone support (CPS) achieved through voice calls, and text messaging (SMS). Our CPS pilot demonstrated significant improvements in viral load through 24 weeks follow-up weeks and improvements in depression and substance use without increased utilization of behavioral health services. As a next step, a full scale clinical trial comparing CPS and SMS is indicated. A SMART design with HIV-positive youth (ages 15-24) at five of our clinic sites will be employed as an innovative, cost-effective, and methodologically rigorous way to explore additional questions to optimize successful interventions and maximize clinical utility and real-world implementation. Contact Marvin Belzer (mbelzer@chla.usc.edu).

CARES

Acute, Recent and Established Youth Living with HIV:

This study will utilize a multi-disciplinary approach of community outreach, behavioral intervention, and prospective surveillance to identify undiagnosed youth infected with HIV. Emerging data on the perinatal "Mississippi baby," a French adolescent with prolonged HIV remission, and adults with acute HIV treatment with early potent ARV have shown that early and sustained viral suppression is associated with a decrease and accelerated decay of HIV reservoirs (VR), which is likely a predictor of long term HIV control and drug free remission. Through innovative point-of-care screening of youth at-risk of HIV, this study will identify 36 acutely infected youth (and 36 recently infected youth as a comparison group) to provide prompt potent cART and follow for treatment response over 24 months. Contact Mary Jane Rotheram (mrotheram@mednet.ucla.edu).

Stepped Care for Youth Living with HIV:

In this randomized controlled trial (RCT), a cohort of 220 seropositive youth will be randomized to one of two conditions (Standard Care vs. Stepped Care) and followed for 24 months. A Stepped Care design will be employed so that youth requiring more support to adhere to the HIV Treatment Continuum (i.e., achieve viral suppression, measured at each four-month assessment) can be upgraded to an increasingly intensive intervention. The Stepped Care condition consists of three levels – Level 1 includes an Automated Messaging and Monitoring Intervention (AMMI); Level 2 includes AMMI plus peer support via online discussion boards; and, Level 3 includes AMMI plus peer support and strengths-based Coaching. Contact Mary Jane Rotheram (mrotheram@mednet.ucla.edu).

Engaging Seronegative Youth to Optimize HIV Prevention Continuum:

The goal of this RCT is to optimize the HIV Prevention Continuum among youth at-risk of HIV using technology and social media-based interventions (e.g., using mobile phones, text messages, online discussion boards and social networking apps). Using a factorial intervention design, participants will be randomized to one of four intervention conditions, including 1) an Automated Messaging and Monitoring Intervention (AMMI), 2) AMMI plus peer support via online discussion boards, 3) AMMI plus eNavigation for linkage and retention in care, or 4) AMMI plus peer support and eNavigation, and followed for 24 months. This study has the potential to inform the efficacy and cost-effectiveness of innovative technology-based interventions for HIV prevention with high-risk youth at a scale that has been rare to date. Contact Mary Jane Rotheram (mrotheram@mednet.ucla.edu).

<u>Funded ATN projects not affiliated with a U19:</u>

Consent2.0

The goal of this project is to examine the effect of consent procedures on adolescents' willingness to participate and parents' willingness to support biomedical HIV prevention trials targeting minor adolescents. In this multi-site study, minor adolescents and parents of minor adolescents will be randomized to one of three consent conditions (required parental consent, optional parental consent, and adolescent self-consent), undergo simulated consent procedures for two types of clinical trials, and indicate how willing they would be to enroll (adolescents only) or support (parents only) the clinical trial. The project will provide empirical data to guide the U.S. FDA, Office of Human Research Protections, researchers, and institutional review boards in their review of research proposals. Contact Amy Knopf (asknopf@iu.edu).

The TERA Project

The goal of the TERA project is to evaluate the efficacy of a Triggered Escalating Real-time Adherence intervention to promote rapid HIV viral suppression among youth living with HIV failing first line antiretroviral therapy. 120 viremic youth between the ages of 13 and 24 will be enrolled and randomized to the TERA Intervention or the standard of care and followed for 48 weeks. The TERA intervention combines several evidence-informed strategies (e.g., phone based problem solving counseling; wireless drug monitoring with texts on delayed dosing) in an escalating intensity, triggered intervention approach that is delivered remotely (through remote counseling, text and phone contact) by an adherence coach for 12 weeks of intensive work. All youth have their adherence documented through AdhereTech's SmartBottle for a full 48-weeks. Outcomes (VLS) at 12 weeks if the primary outcome. Secondary outcomes include 24, 36, and 48 week VLS and EDM adherence at the same time points. This study will provide valuable information. Contact Rivet Amico (ramico@umich.edu).

Work2Prevent (W2P):

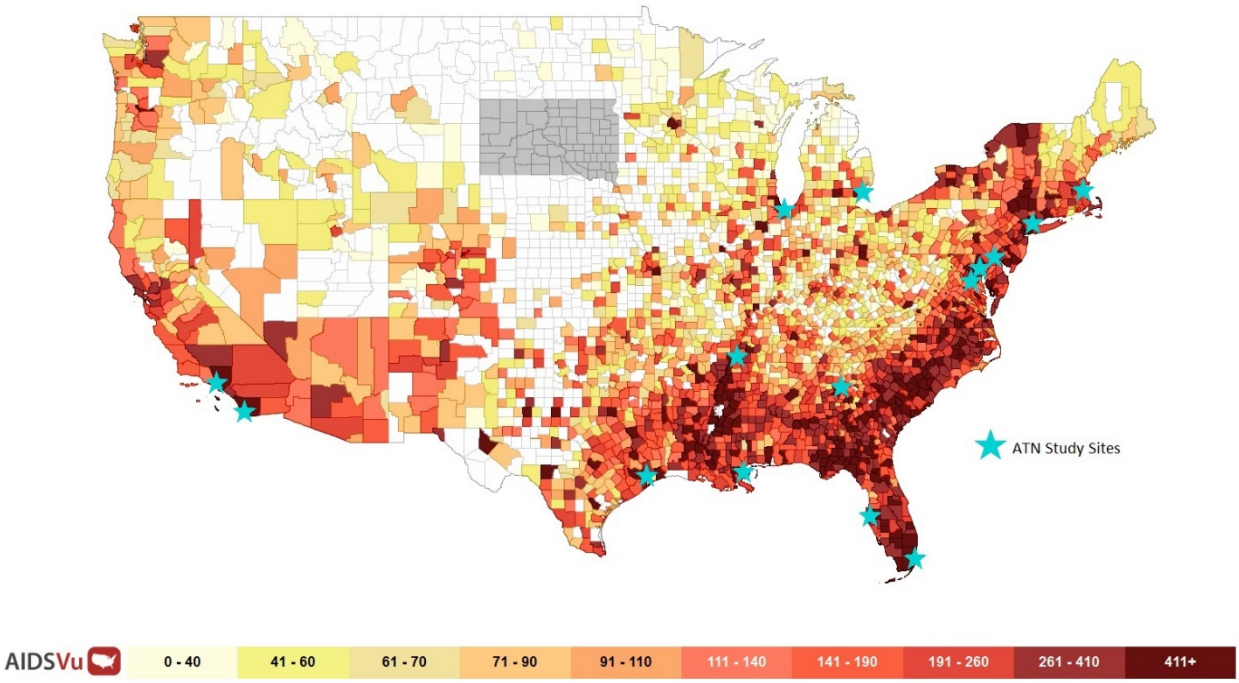
W2P will adapt and pilot-test an effective theoretically-driven employment program for HIV-positive adults (iFOUR) to the needs of at-risk YMSM and young transgender women of color, ages 16-24. Qualitative and quantitative data will provide evidence of the feasibility, acceptability, and preliminary efficacy of the W2P intervention. Primary outcomes include employment, job readiness, and job seeking self-efficacy. Secondary outcomes include reliance on transactional sex work, homelessness/housing instability, food insecurity, and HIV risk behaviors. Contact Brandon Hill (bhill2@bsd.uchicago.edu).

ATN Coordinating Center (U24):

The Coordinating Center provides administrative, statistical, research operations, data management and other expertise to support the ATN. As part of the University of North Carolina at Chapel Hill Department of Biostatistics, we provide extensive analytic capabilities for a wide variety of study designs including sequential multiple assignment randomized trials, adaptive designs, pragmatic trials and comparative effectiveness studies. Involvement with ATN protocols can vary from minimal tracking through full design and operational support. The range of services available includes collaborative protocol development, study design and power analyses, fine-tuning and harmonization of data collection content, data management, training, design and implement protocol-specific quality assurance programs, coordination of laboratory specimens, statistical analyses for project monitoring, presentations and manuscripts, website development and maintenance, and operational support for regulatory submissions. Data management services include use of the Carolina Data Acquisition and Reporting Tool (CDART) for web-based electronic data capture (21 CFR Part 11 compliant) and computer-assisted self-interview, integrated eligibility determination and randomization, real-time data queries, coding, and many other features. Contact Myra A. Carpenter (myra_carpenter@unc.edu).

APPENDIX B

ATN Study Sites



iTech:

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CARES:

Los Angeles
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Scale it Up:

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