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Improving the Youth HIV Prevention and Care Cascades: Innovative Designs in the Adolescent Trials Network for HIV/AIDS Interventions

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Abstract

Dramatic decreases in HIV transmission are achievable with currently available biomedical and behavioral interventions, including antiretroviral therapy and pre-exposure prophylaxis. However, such decreases have not yet been realized among adolescents and young adults. The Adolescent Medicine Trials Network (ATN) for HIV/AIDS interventions is dedicated to research addressing the needs of youth at high risk for HIV acquisition as well as youth living with HIV. This article provides an overview of an array of efficient and effective designs across the translational spectrum that are utilized within the ATN. These designs maximize methodological rigor and real-world applicability of findings while minimizing resource use. Implementation science and cost-effectiveness methods are included. Utilizing protocol examples, we demonstrate the feasibility of such designs to balance rigor and relevance to shorten the science-to-practice gap and improve the youth HIV prevention and care continua.

Keywords: adolescent, behavioral, HIV, methods

Introduction

Dramatic decreases in HIV transmission are achievable with currently available biomedical and behavioral interventions, including antiretroviral (ARV) treatment and pre-exposure prophylaxis (PrEP).[1,2] However, such decreases have not yet been realized among adolescents and emerging adults (ages 12–24; hereafter called ''youth''). For ARVs to have an effect on the epidemic, youth living with HIV (YLWH) must be fully engaged in every stage of the HIV care continuum: diagnosis, linkage to care, engagement and retention in care, initiation of antiretroviral treatment (ART), and viral suppression.[3] Similarly, youth at high risk for HIV infection must be fully engaged in the HIV prevention continuum: routine HIV and sexually transmitted infection (STI) testing, and PrEP knowledge, access, uptake, and adherence when warranted.[4] Although recent descriptive studies have elucidated individual and contextual variables associated with such engagement,[5–10] youth interventions remain understudied.

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Developing and implementing behavioral treatments to improve the adolescent HIV prevention and care continua requires research across the translational spectrum,[11] often referred to as T1–T4 (Fig. 1). Traditionally, T1 refers to the development of new, innovative, and potentially more potent behavioral treatments that evolve directly from basic behavioral and social science findings. T2 research encompasses clinical trials to evaluate intervention efficacy under optimal conditions. T3 research includes effectiveness and implementation trials to test interventions in real-world settings. T4 studies assess the public health impact of implemented interventions.

Until the past decade, the randomized controlled trial (RCT) had been considered the ''gold standard'' in biomedical and behavioral T2 research,[12] including within the youth HIV research agenda. The global HIV epidemic and the economic crises of the past decade have created a useful disruption to this paradigm. Namely, the importance of behavior change in delaying or mitigating disease onset and outcomes has created an urgency for the development of new, cost-effective, and potentially more effective approaches to changing behavior, testing in real-world settings, integration with biomedical and structural interventions, and more efficient implementation of existing, proven interventions in clinical practice and the community.[13,14] Research addressing the needs of youth at high risk for HIV infection and YLWH can benefit from the use of innovative designs beyond the traditional RCT that are efficient, effective, and balance rigor and relevance to achieve these goals across the translational spectrum.

Relatively little attention has been paid to designs, methods, and analytic techniques for early-phase (T1) behavioral translational research.[15] More attention has been focused on the development of study designs and methods for later-phase (T2, T3, and T4) behavioral research; however, here too there is a need to improve study quality, rigor, and efficiency.[16] This emphasis on accelerating the discovery, development, testing, and implementation of effective health-related behavioral interventions is occurring in the context of reduced research budgets and a need for more efficient study designs to lower the costs of large-scale clinical trials and epidemiologic studies.[17] Thus, the purpose of this article is to present an overview of innovative designs across the translational spectrum and demonstrate how the Adolescent Medicine Trials Network (ATN) for HIV/AIDS interventions protocols leverage these designs to efficiently and effectively improve the youth HIV prevention and care continua.

Methods

The ATN currently includes three research programs (or U19s) each with several research protocols and a Coordinating Center (U24) that manages several protocols outside of the three U19 programs. Each U19 supports a research program with a well-defined research focus supported by core infrastructures as well as subject recruitment and enrollment capacity. The CARES program focuses on the integration of low-intensity mobile phone-based intervention strategies and more traditional evidence-based behavioral interventions to operationalize the Centers for Disease Control and Prevention (CDC) treatment guidelines. The iTech program aims at impacting the HIV epidemic by conducting novel, interdisciplinary research on technology-based interventions across the HIV prevention and care continuum for youth. The Scale It Up program emphasizes the implementation of evidence-based interventions focused on improving self-management among youth with HIV and at-risk youth. An overview of several innovative designs for translational behavioral research across the translational spectrum is presented next, and it describes the use of these designs in ATN protocols.

Results

User-centered design (T1)

User-centered, or person-based, designs in the T1 phase of translation have the objective of identifying attitudes and behaviors of the individuals who will be ''targets'' of the intervention to design intervention components that are acceptable and feasible.[18] These study designs are typically utilized in the earliest phases of intervention development but may be considered at subsequent points to assess attitudes of

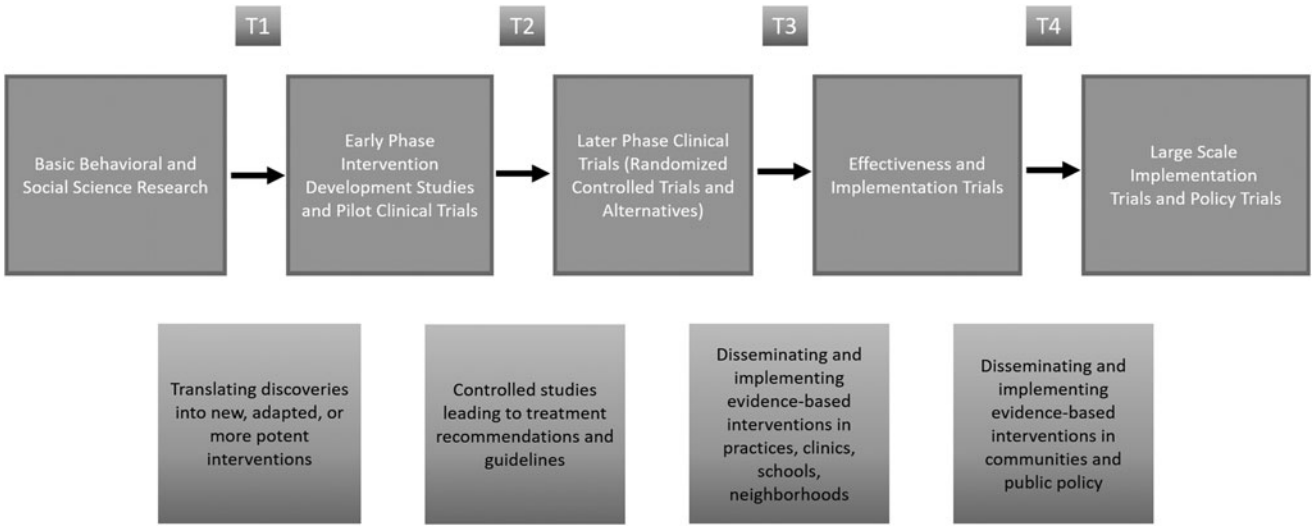

FIG. 1. Translational spectrum of behavioral research.

participants to the intervention to refine components to increase acceptability. The two key elements of the person-based approach are: (i) an iterative development process that gathers substantive feedback on the psychosocial context of users and their perspectives on the intervention's key behavior change mechanisms and (ii) the development of ''guiding principles'' to describe the ways in which the intervention will address behavior changes that are specific to the user's context. The person-based approach is intended to promote user autonomy, competence, and positive experience and relatedness through the health intervention design, components critical to engaging adolescents.[19]

User-centered designs typically employ mixed-methods approaches, involving integration of qualitative and quantitative data to yield ''hybrid insights'' that may inform the development of a human-centered, innovative intervention.[20] Across the ATN, mixed methods are being used to maximize the likelihood of youth adoption of and ongoing engagement in health interventions, a persistent challenge. Three ATN examples of T1 research demonstrate user-centered design for developing new interventions for YLWH. In the CARES program, mixed methods are being used for continuous quality improvement to increase intervention engagement. Mixed methods are critical tools for monitoring technology-based intervention utilization patterns (i.e., quantitative data from paradata) and gathering user feedback (qualitative data) during intervention implementation to inform updates to maximize engagement, and by extension, expected intervention impact. For example, CARES coaching interventions were originally conceived to primarily use digital (text message, social media, voice calls) means for engaging with participants. This was based on prior experiences, with youth being reticent to participate in in-person interventions and some preferring social media engagement. Contrary to this assumption, ongoing qualitative feedback from CARES participants has indicated that youth prefer to engage face-to-face initially to build rapport and initiate a relationship, and then transition to digital engagement over time.

In the iTech program, a user-centered design was utilized in T1 development of Prepared, Protected, and emPowered (P3), a mobile phone app designed to improve PrEP adherence and retention in PrEP medical care among young men who have sex with men (YMSM) and young transgender women who have sex with men (ATN 142). P3 is adapted from a medication adherence app for young HIV-positive YMSM, AllyQuest, that is based on the Social Cognitive Theory and the Fogg Behavioral Model of persuasive technology.[21–23] Figure 2 outlines the purpose of and activities conducted in the planning, design, and development and evaluation of acceptability and feasibility stage, consistent with the person-based approach.

The Scale It Up research program is leveraging a user-center design with mixed methods to develop an implementation intervention to promote evidence-based behavior change communication with youth providers. Thus, even in implementation science studies, user-centered design may be relevant for the development phase. Guided by the implementation science Exploration, Preparation, Implementation, and Sustainment (EPIS) framework,[24] the protocol (ATN 153) assesses provider perceptions of inner context factors (e.g., leadership) and outer contextual factors (e.g., funding) that create barriers and facilitators for the uptake of evidence-based interventions in the ATN sites by using qualitative interviews and surveys of attitudes and organizational climate. These data are utilized to create an implementation intervention (set of implementation strategies) that is tailored to balance fidelity and flexibility for the sites.

Stepped-care intervention designs (T2)

YLWH are heterogeneous, and their needs and ability to achieve desirable HIV-related outcomes (e.g., viral suppression) vary widely. Delivery of a minimum level of support would not be likely to achieve desired outcomes for youth with more complex needs. On the other hand, uniform delivery of the most intense level of intervention may not be necessary, desirable, or cost effective for all youth. The stepped-care intervention design is well suited to address the unique challenges of tailoring interventions to the individual needs of YLWH. The key feature of stepped-care design is to increase the level of intervention systematically until participants reach the desired outcome. Youth are initially provided with a minimum level of intervention. If a youth fails to reach the targeted outcome, the intensity and type of intervention is increased. The stepped-care intervention design has been used for managing other chronic diseases, particularly in mental health care,[25,26] and is an innovative approach for offering tailored intervention in the context of a traditional RCT (T2). Note that in studies of stepped care delivered by real-world clinics or community agencies, the design may be utilized to test T3 effectiveness.

The CARES program is evaluating the merits of a stepped-care intervention for YLWH (ATN 148) who at the time of screening are not virally suppressed, by randomizing these youth to either a Stepped Care or Standard Care (SC) arm. YLWH in the SC arm receive daily motivational short message service (SMS) messages and weekly SMS surveys on their mobile phones to monitor risk and ART adherence. This constellation of services is also Level 1 within the Stepped Care arm. At the first 4-month follow-up assessment, which includes rapid diagnostic tests for STIs and substance use (methamphetamine, opiates, marijuana, and alcohol) and viral load (VL) monitoring with dried blood spots, YLWH on the Stepped Care arm with a VL count >200 are stepped up to Level 2. Level 2 consists of Level 1 services plus online peer support via a private chat room that is accessible only by other study participants. YLWH who remain virally unsuppressed at the next 4-month follow-up visit are stepped up to Level 3, the highest level of support. YLWH at Level 3 continue to receive Level 2 intervention and are also assigned a coach who offers support, links to services, sets goals, and problem solves with the youth, with a particular emphasis on adherence and retention to care. The increasing levels of care offered in the Stepped Care Arm are shown in Fig. 3.

The Triggered Escalating Real-time Adherence (TERA) protocol (ATN 152), under the Coordinating Center, also aims at evaluating the effectiveness of a stepped-care intervention. TERA is a randomized clinical trial (T2) for YLWH who have failed ART, with participants randomly assigned to either the stepped-care intervention or SC. The TERA intervention is an intensive, time-limited (12-week) sequence of ART adherence-supported strategies implemented

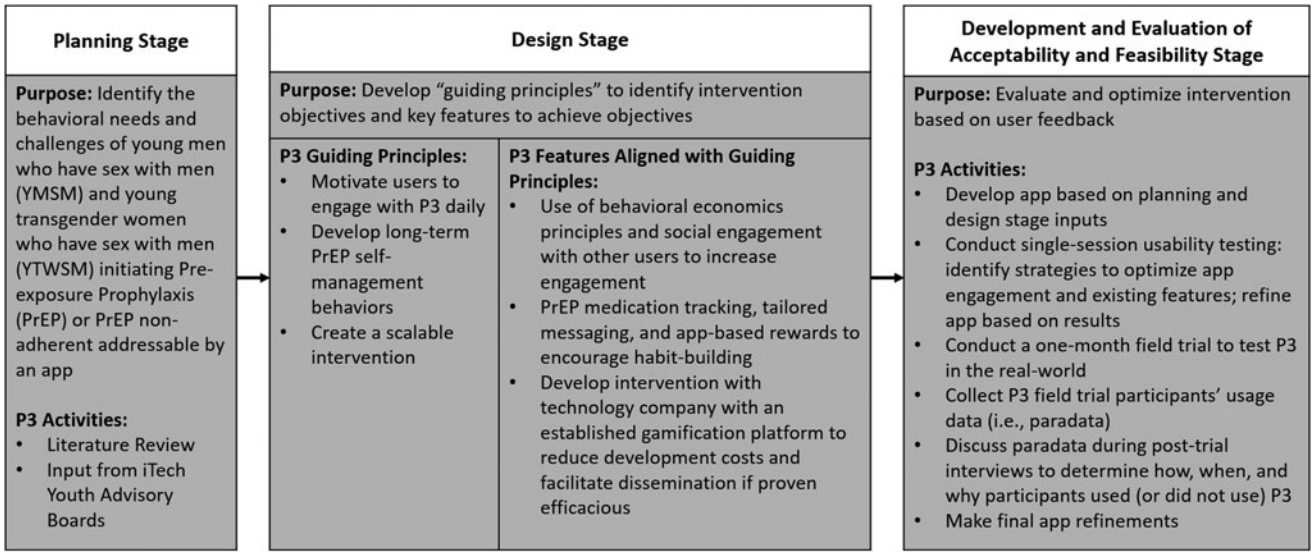

FIG. 2. Example of user-centered design in ATN 142. ATN, Adolescent Medicine Trials Network.

as needed and in increasing intensity on the basis of monitoring of dose-taking from an electronic dose monitoring (EDM) device. Trained counselors work with participants through video-enabled conferencing at three clinic visits and interact via text, phone, and video as needed in real time for missed doses signaled by the EDM device. Specific components of the intervention implemented over the 12-week intervention period are: (i) remote education/preparation through counseling and planning with an assigned adherence coach (on computer at clinic site at baseline and weeks 4 and 12, as needed and as-available between visit coaching sessions); (ii) one-way text alert at dose time when the bottle has not yet been opened for that dosing window; (iii) missed dose two-way interactive outreach text; and (iv) implementation of the coach-outreach (phone, text, remote counseling) triggered by missed doses or as a check-in.

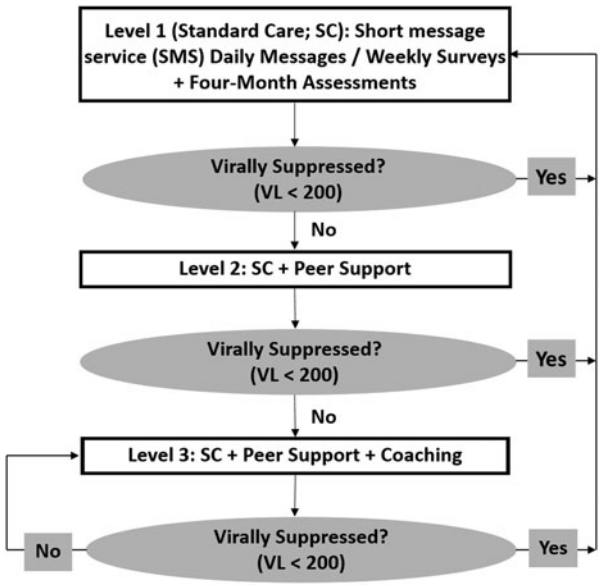

FIG. 3. ATN 148 schematic of increasing levels of care and decision points around VL for stepped care arm. ATN, Adolescent Medicine Trials Network; VL, viral load.

The TechStep (ATN 160) study in the iTech U19 will also utilize a stepped-care design. This trial will evaluate technology-based stepped care to mitigate the risk of HIV acquisition and increase PrEP uptake among trans feminine, trans masculine, and gender non-conforming adolescents and young adults. Participants will initially be randomized to one of three study arms: (i) low-intensity HIV/STI information, transgender resources, and community referrals control arm; (ii) receipt of a text messaging intervention providing daily messages that address the HIV prevention continuum; or (iii) access to a WebApp promoting risk reduction, PrEP uptake, and healthy behavior through virtual peer support, tailored content, self-monitoring, and a resource locator for trans youth. At the 3-month follow-up assessment, participants in the text message arm and the WebApp arm who do not report sexual risk reduction or PrEP uptake will be re-randomized in a 2:1 ratio to be stepped up to e-coaching plus their original intervention (i.e., e-coaching + texts, or e-coaching + app) or remain in their original (text or app) condition for an additional 3 months. Those randomized into the low-intensity basic information arm will remain in that arm for the entire 6-month intervention period.

Adaptive treatment designs (T1, T2, T3)

In traditional RCTs and the stepped-care intervention design, the key elements, such as type of treatment, optimal dosage, and intervention duration, are all pre-determined and held constant throughout the execution of the trial. However, there could be substantial uncertainty regarding the features of the optimal treatment and, hence, designs to develop adaptive treatments (T1) may be preferred in some settings. As opposed to adaptive research designs where the study design is adapted between participants,[21–24] in adaptive treatment designs the intervention strategies are modified within patients systematically to develop tailored treatments that allow the type and dosage of treatment to change according to individual patient outcomes. Thus, changes in the

intensity or type of treatment are not pre-specified as in the stepped-care intervention design. Instead, the adaptive treatment design evaluates multiple treatment alternatives to develop the most efficient and effective treatment.[27] The Sequential Multiple Assignment Randomized Trial (SMART) design can be used to inform the construction of adaptive interventions.[28] SMART is a multi-stage trial where each stage corresponds to a critical treatment decision and randomization takes place at each decision point. It can be used as a rigorous approach to T1 intervention development, but with large sample sizes it can also be powered to test T2 hypotheses.[29] When conducted in the context of real-world settings using strategies that have been shown to be efficacious, the design can be utilized in T3 research as in the example given next.

Within the Scale It Up program, the SMART protocol (ATN 144) utilizes a SMART design with two stages of randomization to compare cell phone support (CPS) and text messaging (SMS) for maintaining better HIV treatment adherence to achieve greater viral suppression. YLWH progress along one of eight possible intervention trajectories with two randomization points. The intervention begins with 24 weeks of CPS or SMS. Based on their 24-week VL (proximal outcome), study participants are randomly assigned to receive one of two conditions within their initial condition. Non-responders (≥200 copies/mL) are randomized to CPS or SMS with incentives; responders (<200 copies/mL) are randomized to a tapered CPS or SC. The design also requires defining a distal outcome (long-term goal). For the SMART protocol, viral suppression at 72 weeks is the primary distal outcome of interest. The SMART design is a cost-effective and methodologically rigorous way to maximize clinical utility and real-world implementation of the resulting adaptive intervention.

Clustered randomized trials (T3, T4)

RCTs are often conducted in community settings to evaluate the efficacy of interventions beyond the traditional research settings for T3 and T4 research. Individuals within a community often share one or more common identifiable features (e.g., geographical area of residence, shared health care provider, and so forth) that may form the basis for grouping individuals into clusters. To analyze interventions in effectiveness settings (T3), cluster (or group) randomized trials (CRTs) may be employed wherein clusters are randomized to the intervention to be evaluated or to a control condition (e.g., standard of care). CRTs may be advantageous from several perspectives, including ethical considerations, enhanced participant compliance, and reduced risk of experimental contamination bias.[30] CRTs may also lower implementation costs and other administrative conveniences. In some situations, the nature of the intervention itself (e.g., group vs. individual) dictates its application at the cluster level.[31]

Design and analysis of CRTs require accounting for possible dependence between individuals within the same cluster. Power and sample size determination for CRTs typically entail considering the intra-cluster correlation (ICC), a measure of within-cluster dependence. Estimates of ICC may be obtained from previous pilot studies.[31] In general, lack of independence between individuals within the same cluster results in a loss in statistical efficiency compared with traditional RCTs where individuals are randomized to treatment and assumed relatively independent. Thus, CRTs tend to require more individuals to achieve the same statistical power. For the analysis of data from CRTs, mixed-effects models are often employed with clusters typically treated as a random effect (but may be fixed depending on the sample nature); whereas the intervention is considered a fixed effect. Alternatively, marginal mean models fit using generalized estimating equations may be utilized to account for within-cluster dependence. Bayesian methods have been developed for the analysis of CRTs for various types of outcomes.[32–34]

Although CRTs have traditionally had two levels (i.e., individuals within clusters), recent designs with additional levels have been developed and employed. For instance, a three-level CRT might involve patients, doctors, and hospitals, with patients who receive care from the same doctor forming one level of clustering, and doctors within the same hospital forming a second level of clustering. Design and analysis considerations for multi-level CRTs are more complicated owing to the nested correlation structure.[35–39] Similar considerations apply for longitudinal CRTs in which trial end-points are measured repeatedly over the course of the trial.[40,41] In addition to statistical power, economic factors such as training cost, travel cost, and data collection and management cost[42] should be considered when designing CRTs.[43,44]

CRT for targeting dyads (T2, T3)

Although their application is not restricted to the study of sexual or romantic relationships, dyadic designs have emerged as a prominent paradigm in the study of couples.[45,46] Their application has been energized by research indicating that main partnerships account for many—possibly most—new HIV infections among gay and bisexual men and the subsequent emergence of Couples HIV Testing and Counseling (CHTC) as a CDC-recommended HIV prevention strategy.[47] CHTC seeks to reduce HIV risk in a relationship by engaging partners in HIV prevention together as a couple.[47,48] The Scale It Up program's We Test protocol (ATN 156) provides an example of the implications of applying a dyadic design within the context of a CRT to develop adjunct intervention components for CHTC to enhance its effectiveness with adolescent-age same-sex male couples.

The We Test study evaluates the comparative-effectiveness (T3) of these adjunct components [video-based couples communication skills, and individual motivational interviewing (MI)-based communication skills] in a series of CRTs to produce an optimized treatment package. Both partners in each couple must indicate male sex and birth and gender identity. In addition, both partners must be 15–20 years old (maximum age difference between partners is 3 years) and at least one partner in the relationship must be HIV negative. Given these eligibility criteria, the data between partners are exchangeable, that is, there is no variable that systematically distinguishes between partners-within-couple. (e.g., a dataset comprising heterosexual couples is distinguishable on gender identity.) Exchangeability has implications for research questions and data analysis.[49] In distinguishable dyads, research questions can be framed in terms of ''partner–type'' (e.g., ''Does relationship investment reported by wives predict

their husbands' mental health?''). Such associations can be quantified by using a Pearson's correlation coefficient in which the sample size is the number of couples. In exchangeable dyads, the inability to systematically distinguish between partners-within-the couple prevents the use of correlation coefficients. Instead, partner similarity must be evaluated by using the ICC or Cohen's κ.

Although the intervention is delivered to the couple, the primary outcomes (i.e., sexual HIV transmission risk behavior, PrEP uptake, and incident gonorrhea and chlamydia infection) of We Test are re-conceptualized at the individual level. As a result, the primary effect of the intervention could be evaluated by using a repeated-measures analysis of variance approach where treatment is specified as the grouping variable and partner responses are nested within the couple. (This analytic approach can be adapted to non-normal outcomes via generalized linear models.)

In contrast, analyses of putative mediators assessed at the individual level (e.g., individual assertive communication skills) will utilize the Actor–Partner Interdependence Model (APIM) framework.[49] The APIM is a standard approach to assessing associations between an individual's scores on a predictor and their own outcome score (actor effects) as well as their partner's outcome score (partner effects). Data from We Test 2.0 will be used to evaluate whether the effects of the couple-level intervention on individual-level outcomes are mediated by indirect pathways involving both actor and partner effects of the putative mediator variable.

Dynamic wait-listed design (T4)

In implementation research (T4)—with its broad focus on strategies for making established interventions and programs work when delivered in community service settings[24]—adaptations of the standard CRT are often required. One such adaptation is the dynamic wait-listed design (DWLD), as used in the Scale It Up program's Tailored Motivational Interviewing (TMI) protocol (ATN 146). TMI's overarching aim is to evaluate the effect of the TMI implementation intervention on the competence of MI delivery among community-based providers (physicians, nurses, psychologists, social workers, and paraprofessional staff). Individual providers could not be randomized due to the risk of contamination within sites, and for practical reasons, only 11 sites could be recruited.

To address these features, the DWLD[50,51] was used. The DWLD—closely related to the stepped-wedge design[52,53] and also referred to as a rollout randomized implementation trial[54]—is a crossover design where each cluster ultimately receives both the control and experimental interventions.[55] With a modest number of clusters measured across both baseline and intervention phases, the DWLD can provide evidence for evaluating intervention effects.

In TMI, the 11 sites, at the same point in time, began a longitudinal baseline (i.e., control) phase, with the MI competence outcome assessed for each provider across sites on a quarterly basis. After 3 months (i.e., two measurements of MI competence), two sites were randomly selected to transition from the baseline phase to the implementation phase. In the implementation phase, delivery of MI training and coaching was initiated, and assessments of MI competence continued for all sites and providers. After 2 months, two additional sites were randomly selected to begin the implementation phase. This process continues until all sites have initiated their MI implementation phase. A strength of the DWLD is that it provides two tests of the TMI implementation intervention. First, across sites, MI competence should be higher during the implementation phase relative to the baseline phase, which, given repeated measurements in each, can include comparisons of mean levels as well as rates of change. Second, at a given point in time, MI competence should be higher for sites in the implementation phase relative to the sites that remain in the baseline phase. Subsequent randomizations are also possible. After 1 year of implementation, each site is re-randomized to an intervention that is designed to increase sustainability (Communities of Practice or Communities of Practice + Internal Facilitation), with MI competence measurements continuing for an additional year.

Pragmatic trial designs (T3, T4)

Pragmatic trials are a type of RCT designed to test the effectiveness of an intervention (e.g., drug or therapy) when used in routine clinical and community settings as in T3 and T4 research.[56] Evidence from pragmatic trials can inform policy and clinical decisions about the real-world effect of an intervention. In contrast, efficacy or explanatory trials assess the effect of an intervention in an ''ideal'' setting where administration of the intervention is carefully controlled, adherence is closely monitored, and trial participants are selected from a homogeneous population. The degree to which a trial is pragmatic versus explanatory can be assessed by considering a variety of domains, including: eligibility, recruitment, setting, organization, intervention delivery, adherence, follow-up, primary outcome, and primary analysis.[57,58]

To ensure generalizability of study results, pragmatic trials typically minimize eligibility criteria (e.g., all patients in a clinic), whereas efficacy trial participants are often selected from a more homogeneous population.[59] Efficacy trials typically require informed consent and financial incentives for participation, which can limit generalizability of study results to the population of interest; whereas pragmatic trials often utilize waivers or other modifications of informed consent, and may not collect data from individual participants with a financial incentive. Pragmatic trials often seek to minimize participant and provider burden regarding data collection as well as frequency and duration of study visits to a clinic or study site. Pragmatic trials typically select important outcomes such as death or hospital admissions that are simple to evaluate, therefore minimizing potential missing outcome data and ascertainment bias.

Routinely collected electronic health care records (EHR) are often useful in the conduct of pragmatic trials.[60,61] EHR can be used to identify individuals who may potentially participate in pragmatic trials. Utilizing EHR can reduce cost and effort associated with data collection and outcome assessment compared with traditional efficacy trials. For example, baseline histories and standard laboratory data may be readily available from a participant's EHR, obviating the need for data collection by the study team conducting the trial. Likewise, EHR can also be used for assessing trial outcomes at a low cost, with no additional burden on trial participants or their health care providers. For instance,

currently the ATN is developing a protocol (ATN 162) to monitor HIV prevention and care continua components by using electronic data systems from the ATN participant recruitment venues. This EHR protocol will: (i) describe the current status of the youth HIV prevention and care continua; (ii) monitor prevention and care continua; (iii) provide a foundation for pragmatic clinical trials and intervention integration; and (iv) inform strategic planning for the ATN.

Hybrid designs

Though user-centered designs are typically utilized in T1 translation, RCTs and adaptive designs in T2, and stepped care and CRTs in T3 and T4, hybrid designs, which cross translational phases, can minimize the science-practice gap and lower cost by efficiently combining translational aims across the spectrum. For example, SMART designs bridge T1 and T2 as they can answer questions about intervention development but often include sample sizes that are consistent with T2 studies. SMART designs can also be T3 studies if implemented in real-world settings (e.g., ATN 144), and they can be used to develop adaptive implementation interventions in T4. Efficacy-effectiveness hybrids integrate clinical trials in real-world settings with diverse populations and limit exclusion criteria to bridge T2 and T3.[62] For example, in the CARES program, protocol ATN 149 tests the efficacy of technology-based interventions that are integrated into real-world community-based settings that are consistent with an effectiveness trial. The study operationalizes CDC guidelines for standard prevention services with repeat testing for HIV and STIs but using rapid diagnostic tests and same-day treatment in these real-world settings.

Effectiveness-implementation hybrids address the effectiveness of an intervention (T3) as well as its implementation (T4), but the type of hybrid design determines the study's primary emphasis of effectiveness or implementation.[63] In a Type 1 hybrid, effectiveness aims are primary and implementation aims are secondary (e.g., understanding the context of implementation while primarily testing effectiveness). In a Type 2 hybrid, effectiveness and implementation aims are equally resourced. In a Type 3 hybrid, implementation is primary and effectiveness is secondary (e.g., testing an implementation intervention while monitoring patient outcomes). The Scale It Up program, with its implementation focus, includes all three types of effectiveness-implementation hybrids. The TMI protocol (ATN 146) described earlier is a Type 3 hybrid where the testing of an implementation intervention is primary, as is understanding the context of implementation with the EPIS model[24] (ATN 153), but the measurement of patient effectiveness outcomes will also be collected as a secondary outcome through EHR. The Young Men's Health Project (YMHP; ATN 145) is a Type 2 hybrid trial where both the effectiveness aim (intervention effect on sexual risk and substance use) and the implementation aim (studying the context of implementation by using site-based clinic staff and supervisors) are primary. ATN 144 (SMART) is a Type 1 hybrid where the primary focus is effectiveness of sequencing of treatments on VL and the secondary focus is understanding the context of implementation within the EPIS model.

Another ATN protocol, managed by the Coordinating Center, utilizes a hybrid design, which is Planning4PrEP (ATN 155). This protocol focuses on integrating PrEP into family planning services in Title X clinics in the southeast United States. Phase 2 of this two-phase protocol entails a hybrid Type 1 effectiveness design to develop, test, and evaluate PrEP implementation plans that are unique to three different Title X clinic types.

Cost-effectiveness

No single design or approach can be used to answer economic questions regarding cost-effectiveness. Economic studies undertaken alongside clinical trials should be designed based on the study hypotheses, intervention tested, and the clinical data collection protocol, and they are usually conducted as part of T3 and T4 trials.[64] However, there are two critical tasks that must be undertaken for every economic study: (i) measuring and costing the resources used to deliver the intervention, and (ii) assuring that the study will capture all relevant economic benefits that differ for the intervention and control population.[65] The first task, measuring the cost of delivering the intervention, requires a detailed assessment of training protocols, capture of resources (time and personnel), and collection of site-specific data for costing information. For certain ATN protocols, study expenditure records are combined with site-specific costing data collected by using the approach described by Kim et al.[66] The second task is to identify the economic benefits relevant to each study population. Explicating the economic benefits has to be carefully tailored to the outcome specified in the primary hypothesis.

For example, the Scale It Up program's YMHP (ATN 145) aims at preventing HIV transmission with a four-session behavioral intervention, and it measures differences in behaviors associated with HIV transmission as the primary outcome. The economic benefits from this intervention are expected to accrue well beyond the time horizon of the study. To capture this benefit, a Markov model[67,68] will be utilized to predict the economic benefits associated with behavior changes over time and the resulting reductions in HIV transmissions. This model incorporates final study efficacy estimates, combined with epidemiological data on the risk of HIV transmission and the ''Basic Model Inputs for Cost Effectiveness'' defined by the CDC.[69] This approach is especially appropriate for studies on the behavior of young individuals in whom early behavior change may be expected to result in benefits that can last for years after the study.

The detailed approach to the economic study costing process includes several distinct steps. The first step is to fit economic resource use data collection to the clinical study design (timing, design, and variable choices).

Next, we identify cost drivers, process measures, and standard cost weights that fit the design. In the third step, we design one or more simulation models to estimate the cost and clinical outcomes of the intervention. Subsequently, study details are specified, including: (i) identifying participant process and outcomes variables required; (ii) mixed-methods data collection for costing the intervention; (iii) prospective data collection and archival data analysis for cost drives of participant resource use differences; and (iv) data analysis to identify the cost of intervention and cost of participant outcomes. The results are reported for three separate types of costs: the cost of the intervention; medical care cost

Table 1. Biobehavioral Research Study Designs with Examples from the Adolescent Medicine Trials Network (ATN)

Study design	*Translational research continuum classification*	*ATN study*
User-centered design	T1	ATN 142: P3 (Prepared, Protected, emPowered)—Promoting PrEP Adherence through a Social Networking, Gamification, and Adherence Support App
Stepped-care intervention design	T2	ATN 152: TERA (Triggered Escalating Real-time Adherence), ATN 160: TechStep (Technology-based Stepped Care to Stem Transgender Adolescent Risk Transmission)
Stepped-care intervention design	T2, T3	ATN 148: Optimizing the HIV Treatment Continuum with a Stepped Care Model for Youth Living with HIV
Randomized factorial design	T2, T3	ATN 149: Engaging Seronegative Youth to Optimize the HIV Prevention Continuum
Adaptive treatment design	T1, T2, T3	ATN 144: SMART—Adaptive Antiretroviral Therapy Adherence Interventions for Youth Living with HIV through Text Messaging and Cell Phone Support Embedded within the Sequential Multiple Assignment Randomized Trial Design
Clustered randomized trial	T3, T4	ATN 156: We Test—Enhancing Sexual Safety: Couples' Communication and HIV Testing Among YMSM
Dynamic wait-listed design	T4	ATN 146: Tailored Motivational Interviewing (TMI)
Pragmatic trial design	T3, T4	ATN 162: Electronic Health Records Continuum of Care (EHR COC) protocol
Hybrid design—type 1		ATN 144: SMART; ATN 155: Planning4Prep—Integrating PrEP into Family Planning Services at Title X Clinics in the Southeast; ATN 156: We Test
Hybrid design—type 2		ATN 145: Young Men's Health Project—Comparative Effectiveness Trial of Clinic-Based Delivery of an HIV Risk Reduction Intervention for YMSM
Hybrid design—type 3		ATN 146: Tailored Motivational Interviewing (TMI)

ATN, Adolescent Medicine Trials Network; PrEP, pre-exposure prophylaxis; YMSM, young men who have sex with men.

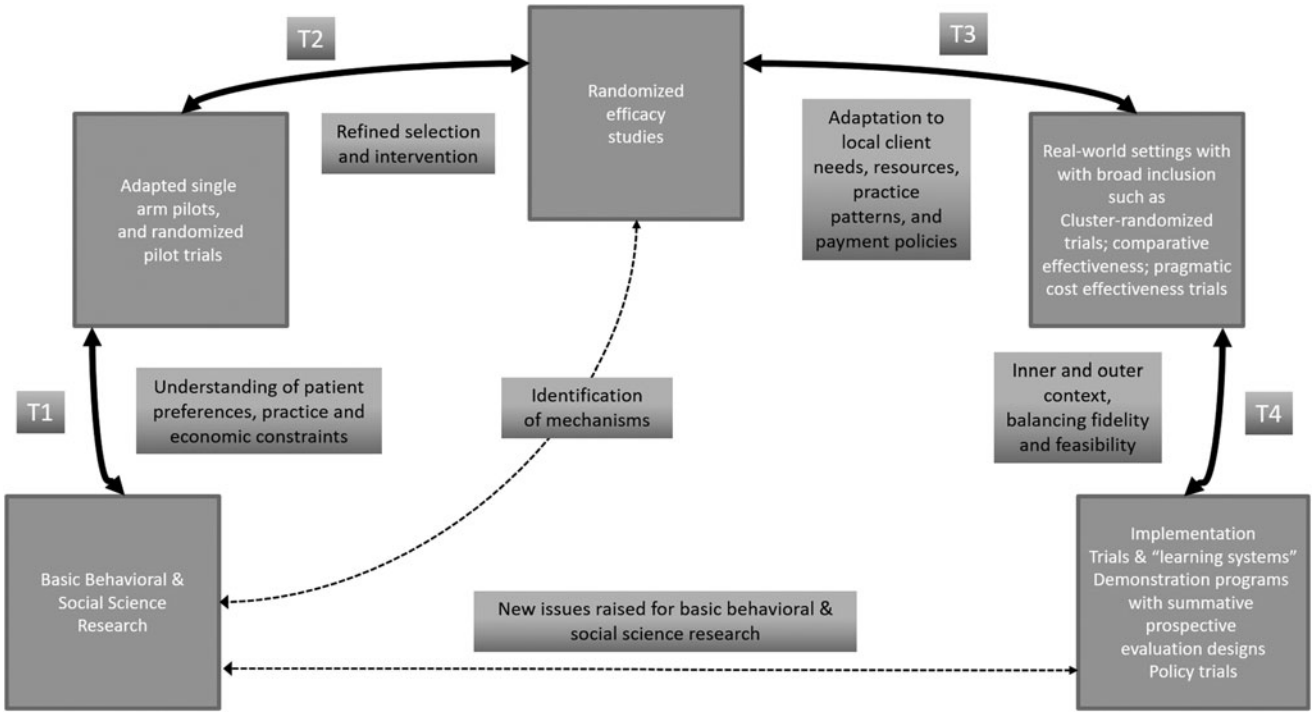

FIG. 4. New translational behavioral research model to guide adolescent HIV research agenda.

differences between treatment groups; and long-term cost estimates from the simulation models, including mean cost per patient and incremental cost-effectiveness ratios (ICERs). The study ICER is calculated by using the formula: $(\text{Cost}_{\text{GroupA}} - \text{Cost}_{\text{GroupB}})/(\text{Clinical Outcome}_{\text{Group A}} - \text{Clinical Outcome}_{\text{Group B}})$.

For example, if the clinical outcome is suppressed VL for the study period, then the ICER represents the cost per additional patient with suppressed VL in the intervention group.

Evaluating cost-effectiveness is an important objective of many ATN studies and is a primary aim of the ATN Modeling Core. Using a microsimulation model of adolescent HIV disease progression, patterns of care, and treatment outcomes, the Modeling Core evaluates the economic and clinical effect of interventions evaluated within ATN trials. Model outcomes will include short-term survival and costs, calibrated to trial results, as well as projected life expectancy and lifetime per-person costs, allowing us to calculate ICERs and compare interventions. The overall goal of these analyses is to leverage existing ATN data and translate emerging ATN data into relevant policy recommendations to improve care for young people with HIV.

Discussion

The health care and economic crises of the past decade have created a useful disruption for behavioral intervention research. Given the important role of behavior change in improving the youth HIV prevention and care continua, it is urgent that new, potentially more effective approaches to changing behavior be developed and tested in real-world settings, and that existing, proven interventions be more widely implemented in clinical practice and the community. Biobehavioral intervention research can benefit from the use of innovative designs that are efficient and effective and that balance rigor and relevance to achieve these goals across the translational spectrum.

Utilizing the various designs along the translational spectrum is especially relevant for evaluating interventions to disrupt the HIV epidemic in youth. Prevention and treatment of HIV in adolescents is complex and necessitates a diverse set of considerations when designing studies. The HIV epidemic in adolescents in the United States is concentrated across different subpopulations, including gay, bisexual, and transgender individuals, as well as certain racial/ethnic subgroups and particular geographic regions. Thus, study designs are needed to determine optimal behavioral, biomedical, and/or structural approaches to decreasing HIV incidence and improving the treatment continua in these subpopulations.

We have mapped protocol design examples from the ATN research portfolio to points on the translational spectrum (Table 1; Fig. 1), but it is clear that specific designs do not perfectly map on to a single point on the translational spectrum and may be used for different purposes across the spectrum. For example, SMART designs are utilized to develop adaptive treatments, and intervention development is often considered a T1 task. However, individual components may be compared in a T2 framework, and sequences of efficacious intervention strategies may be tested in real-world settings within T3. Hybrid designs may combine unique features of several designs for more rapid translation. As a result, we propose an alternative to the typical biomedical translational model (Fig. 4). This model demonstrates the recursive features of the translational process. Although it is not expeditious to draw arrows between every box, results from one translational phase may inform another later or earlier in the process, and depending on those results, investigators may need to return to earlier phases or continue to later phases.

Team science efforts are necessary to solve the complexity of modern health concerns, including those of YLWH.[70] The ATN brings together traditional behavioral science disciplines with epidemiology, statistics, and mathematics; clinical medicine and public health; qualitative and mixed methods research; engineering and computer science; and communication science, information science, and bioinformatics. The team science approach that supports the cross-fertilization of concepts is critical to the continued development of innovative methods to move behavioral science forward and achieve the Network's adolescent HIV research agenda.

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