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Innovative Approaches for Minor Consent: Consent 2.0

A Multi-Center Study of the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN)

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REQUIREMENTS FOR SITE PARTICIPATION IN PROTOCOL

Each enrolling site should have the following minimum capabilities:

- Ability to enroll in a 15 month period 36 adolescents (18 natal males, 18 natal females) and approximately 36 parents of adolescents (parents of 18 natal male adolescents, parents of 18 natal female adolescents);
- Have adequate private space to administer Computer Assisted Self-Interview (CASI);
- Have adequate private space for the Study Coordinator to conduct a debriefing interview; and
- Ability to designate Study Coordinator, or other research staff (RS), time for recruitment of subjects, subject management, and completion of study-related data collection forms

STUDY MANAGEMENT

Before the recruitment and enrollment of participants, the participating ATN study sites must have the protocol approved by the governing Institutional Review Board (IRB). In addition, ATN study sites must receive protocol registration approval from the ATN Coordinating Center (CC). All original approved documents must be maintained at the clinical site.

All queries for this protocol should be sent to the IU project team using the ATN Protocol Query and Notification System (QNS) accessible via the ATN website (https://www2.cscc.unc.edu/atn/). Dr. Knopf or the Consent 2.0 Program Manager will respond to queries generally within 48 business hours via the ATN QNS and copy the other team members. The Consent 2.0 Program Manager, with the help of other study staff and/or NICHD, if necessary, will answer general protocol implementation, eligibility, and data collection queries. The Protocol Chair or her designee will respond to study and participant management, exemptions and/or adverse event queries. Queries and replies will automatically be archived at the ATN CC. The Consent 2.0 Program Manager will post those queries deemed relevant to all sites on the ATN website, where they will be available for future reference.

This study will use Qualtrics to collect study data via the internet. All questions related to the Qualtrics survey and screening survey should be directed to the IU Data Manager (Carla Kettler, ckettler@iu.edu) and the Consent 2.0 Program Manager (Becca Baker, bbaker11@iu.edu) during regular business hours, Monday-Friday 8:00am-4:00pm ET. After hours Qualtrics questions should be directed to Dr. Amy Knopf at asknopf@iu.edu. Qualtrics questions/issues that do not require immediate attention should be sent via the ATN QNS.

For protocol or site registration issues or general ATN-related questions, contact ATNhelp@unc.edu. This account will be monitored on a regular basis during normal business hours.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AIDS	Acquired Immunodeficiency Syndrome
AMTU	Adolescent Medicine Trials Unit
ANOVA	Analysis of variance
ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
CASI	Computer Assisted Self-Interview
CC	Coordinating Center
CFR	Code of Federal Regulations
CRF	Case Report Form
CO	Colorado
DHHS	U.S. Department of Health and Human Services
EC	Ethics Committee
eCRF	Electronic CRF
FDA	U.S. Food and Drug Administration
FIMSA	Federal Information Security Modernization Act
FIPS	Federal Information Processing Standards
FL	Florida
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
ICH	International Conference on Harmonization
ID	Identification
IL	Illinois
IRB	Institutional Review Board
IT	Information Technology
IU	Indiana University
LGBTQ	Lesbian, gay, bisexual, transgender, questioning
MD	Maryland
MTN	Microbicide Trials Network
NICHD	National Institute of Child Health and Development
NIDA	National Institute on Drug Abuse
NIMH	National Institutes of Mental Health
NIST	National Institute of Standards and Technology
OHRP	Office of Human Research Protection
PAMAB	Pediatric, Adolescent, and Maternal AIDS Branch
PGP	Pretty Good Privacy
PI	Principal Investigator
PrEP	Pre-exposure prophylaxis
QA	Quality Assurance

QNS	Query and Notification System
RS	Research Staff
SID	Study Identification Number
SIS	Study Information Sheet
SMC	Study Monitoring Committee
STI	Sexually transmitted infection
STRC	Study Team Review Committee
TDF-FTC	tenofovir-emtricitabine
UBACC	UCSD Brief Assessment of Capacity to Consent
UCSD	University of San Diego
UE	Untoward Event
US	United States
WTP	Willingness to Participate
WTS	Willingness to Support
YMSM	Young men who have sex with men
YWSM	Young women who have sex with men

STUDY ABSTRACT

DESIGN: This study will use CASI completed by all participants and a detailed debriefing interview completed for a subset of participants to assess high-risk minor adolescents' willingness to participate in and parents willingness to support their teen's participation in two hypothetical trials using simulated consent processes. The two hypothetical trials are modeled after ATN 113 and HPTN 077.

The purpose of this study is to examine how the consent process affects the acceptability of participation in biomedical HIV prevention trials, from the perspective of behaviorally high-risk minors and the parents of minor adolescents.

DURATION: Study participation will last approximately 60 minutes on a single day with no follow-up. Participants who agree to participate in the debriefing interview will require an additional 45 minutes immediately following the completion of the main study procedures.

SAMPLE SIZE : Approximately 144 (36 per study site) high-risk minor adolescents and 144 (36 per study site) parents of adolescents will be recruited for participation in this study. Of note, the adolescents and parents will not be parent-child dyads; they will be unrelated. A subset of 24-32 (6-8 per study site) adolescents and 24-32 (6-8 per study site) parents will be selected to participate in the debriefing interview.

POPULATION: This study will recruit adolescents between ages 14-17, inclusive, who are able to read and speak English, who have a negative or unknown HIV status; and who have engaged in high-risk sexual activity in the last 12 months.

The study will also recruit adults who are able to read and speak English and who are parent or guardian to an adolescent who is between ages 14-17, inclusive.

Adolescents and parents will be recruited from four U.S. cities: Baltimore, MD; Chicago, IL; Denver, CO; and, Tampa, FL. These cities have diverse populations, high rates of incident HIV infection among adolescents and young adults, and/or demonstrated success in recruiting minor adolescents for biomedical HIV research.

RANDOMIZATION:

Adolescents will be randomized in a 1:1:1 ratio into 1 of the 3 consent conditions using block randomization with block size k=3 (so that in every 3 subjects, exactly 1 is allocated to each condition). The randomization will be stratified by study site and sex assigned at birth. Within study site, sex assigned at birth, and consent condition, the order in which the hypothetical trials will be presented to adolescents will be block randomized with block size k=2. A subset of 6-8 adolescents (3-4 males and 3-4 females) at each site will be selected for participation in the debriefing interview.

Enrollment of parents will be restricted to approximately 15 parents of adolescent natal males and 15 parents of natal adolescent females at each study site. Parents will indicate the acceptability of each of the three consent conditions for each of the two hypothetical trials. Independently of the gender strata, the order of hypothetical trial presentation will be block randomized with block size k=2. Separately for each hypothetical trial, the order of evaluation of the three consent conditions will be randomized so that each ordering is equally likely. A subset of 6-8 parents at each site (for total of 24-32) will be selected for participation in the debriefing interview.

SPECIFIC AIMS:

1. Describe how consent conditions influence high-risk minor adolescents' WTP in a hypothetical biomedical HIV prevention trial.

2. Describe how consent conditions affect parents' WTS a hypothetical biomedical HIV prevention study.

3. Describe the effects of the study agent (stage of development and method of delivery) on high-risk minor adolescents' WTP and parents' WTS a hypothetical biomedical HIV prevention trial.

STUDY PROCEDURES

Potential participants will be recruited from clinical settings and HIV testing centers, or self-screen online. Potential participants will take a short CASI screening survey to determine eligibility. All eligible participants will provide contact information to establish a study visit appointment. Those eligible and screening in-person will either participate on the same day as the screening, or, if unable to stay, they will be contacted to establish a study visit appointment. Eligible participants who screen online will also provide their contact information to establish a study visit appointment.

Study participants will attend an in-person session at their respective AMTU. During the session, they will complete a CASI that collects demographic, social, behavioral, and attitudinal measures.

All study participants will undergo a simulated consent process for each of two hypothetical studies modeled after ATN 113 and HPTN 077. Procedures are slightly different for parents than for adolescents, so each group is described separately below:

Adolescent Participants: First, the adolescent participant will complete a demographic CASI. *For each hypothetical trial,* RS will lead the participant through a simulated consent process consistent with their randomized consent condition. Then, the participant will complete a CASI assessing WTP and will work with RS to complete the UCSD Brief Assessment of Capacity to Consent (UBACC). After the second UBACC, the adolescent will complete overall WTP, medical mistrust, and end of study questions.

Parent Participants: *For each hypothetical trial*, RS will review the informed consent forms with the parent. The parent will complete a CASI with three vignettes that describe each of the three possible consent conditions. Parents will rate the acceptability of each vignette. Then, the participant will work with RS to complete the UCSD Brief Assessment of Capacity to Consent (UBACC). After the second UBACC, the participant will answer demographic questions, medical mistrust, and end of study questions.

A subset of 6-8 adolescents and 6-8 parents per study site will complete a debriefing interview assessing adolescent and parent perspectives on the various consent conditions in greater depth, and to better understand the role of study features, family, and adolescent characteristics in willingness to

participate/willingness to support the hypothetical research studies.

MONITORING: Routine team monitoring of any adverse impact of the study will rely on the ATN Query & Notification System (QNS), a real-time, web-based interactive reporting system. Sites will record and enter in the ATN QNS, all untoward events associated with study participation, which will be reviewed on the Study Team Review Committee's monitoring calls. Routine team monitoring of protocol deviations will occur through Qualtrics. RS will enter any deviations into the Protocol Deviations Survey, which will automatically notify the central IRB site PI, Dr. Amy Knopf, and her study team.

STUDY SCHEMAS

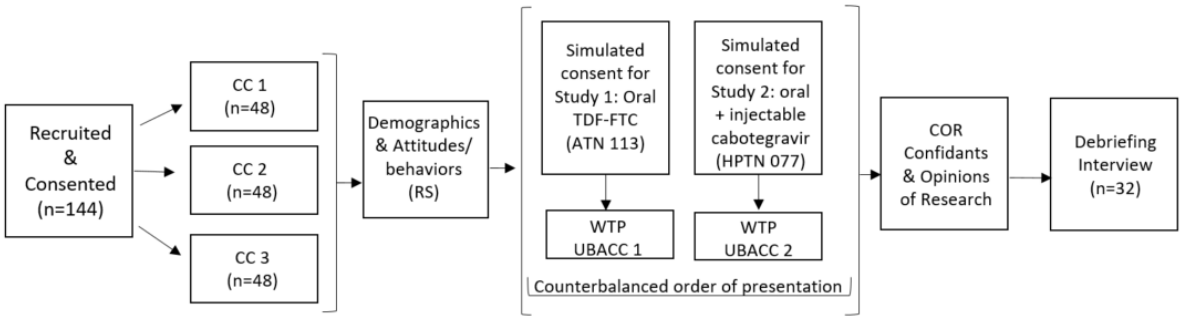

Figure 1A. Study schema, adolescent participants

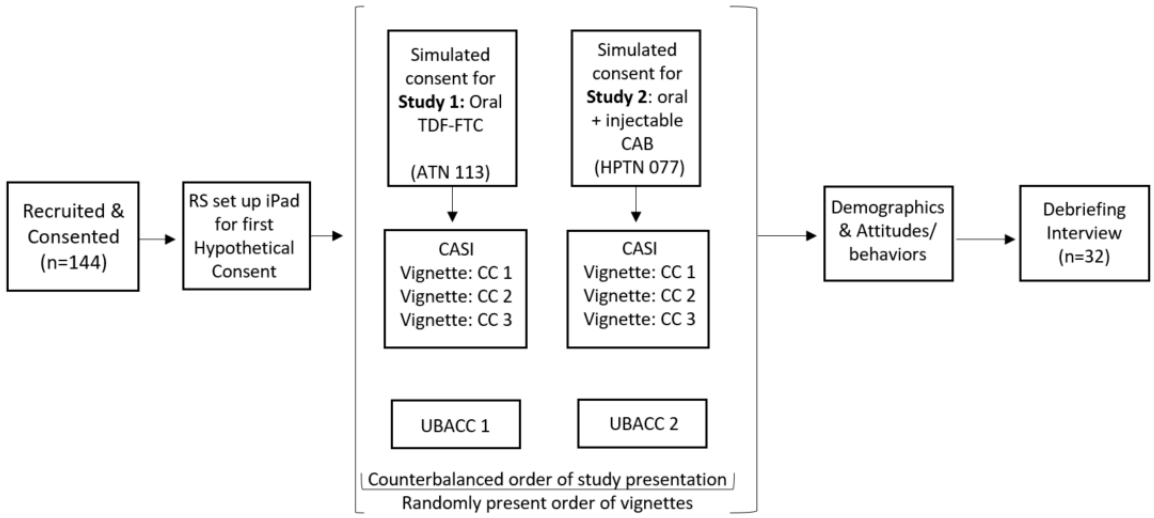

Figure 1B. Study schema, parent participants

Legend for both figures:
CC – Consent Condition
CC 1: Adolescent self-consent
CC 2: Adult permission required
CC 3: Parental permission required
CAB – Cabotegravir (an HIV treatment medication)
CASI – Computer assisted self-interview
RS- Research Staff
WTP – Willingness to participate in the study
UBACC – UCSD Brief Assessment of Capacity of Consent

1.0 INTRODUCTION

1.1 Background

American youth are disproportionately affected by the HIV epidemic, accounting for an estimated 26% of all new HIV infections. Young men who have sex with men (YMSM), and young women of color are at especially high risk. Together these two groups comprise 86% of all incident infections among persons aged 13-24.[1] New biomedical prevention approaches have dramatically decreased the risk of HIV infection in adults. One particularly promising approach is pre-exposure prophylaxis (PrEP), which involves prescribing an HIV treatment medication to those at high-risk of acquiring HIV. PrEP with once daily dosing of oral tenofovir-emtricitabine [TDF-FTC] has demonstrated 95% efficacy in adherent adult users.[2, 3] The U.S. Food and Drug Administration has approved oral PrEP with TDF-FTC for adults aged 18 and older. There are currently no published data on the safety and efficacy of PrEP with TDF-FTC for minor adolescents, so it is not yet approved for prevention in this population.

One reason for the evidence gap is a well-described reluctance to include minors in biomedical HIV prevention research, because doing so presents ethical complexities.[4, 5] There are three basic ethical principles that govern research with human subjects: respect for persons, beneficence, and justice.[6] The first of these principles is the most difficult to operationalize in research with minors. Respect for persons requires treating individuals as autonomous actors, and protecting those with diminished autonomy. For decades, individual autonomy has been marked by attaining the legal age of consent to medical treatment or procedures,[7] which is generally the age of majority, unless the treatment is for a socially stigmatized condition. Thus, in most research, minor adolescents fall into the category of those with diminished autonomy who require additional protection beyond those afforded to all human subjects. Parental permission is a cornerstone of these additional protections for minor research subjects.[8] The requirement for parental permission is founded on several assumptions. The first is that children lack the capacity to understand and weigh the risks and benefits of research, and may make decisions that are not in their own best interest. The second assumption is that parents have a fundamental right to make decisions about their children's health and welfare, and to have those decisions reflect their own values. The third assumption is that parents will act in the best interest of their children.[8]

Connection to parents is often protective against a variety of risk behaviors,[9] and disclosure to parents has been shown to be associated with a lower risk of HIV acquisition among YMSM.[10] However, requiring parental permission forces the disclosure of sexual behavior, and in many cases, sexual orientation. Research demonstrates that requiring parental permission can delay treatment of stigmatized conditions, such as addiction, pregnancy, and sexually transmitted infections (STI) when adolescents fear social harms due to their disclosure to parents.[11] Delays in seeking treatment pose risk to the minor and, in some cases, to the public.[8] Thus, for decades states have allowed minors to consent to the diagnosis and treatment of STI,[12] and, because of the way "children" are defined, these exemptions extend to research. Federal regulations allow minors to consent, without parental permission, to research that involves the same treatments or procedures to which they are allowed to self-consent in the jurisdiction in which the proposed research will take place.[8] The allowance for minor self-consent is aligned with a body

of evidence that suggests adolescents are capable of making medical decisions that are comparable to the decisions of adults.[13] It is also reflective of the findings of two studies[14,15] in which the institutional review boards (IRBs) changed consent processes midway through, creating a natural experiment of the recruitment effect of requiring parental consent. In both of the studies it was found that self-selection bias toward lower-risk adolescents once parental consent was required for participation.

Investigators and IRBs must balance protective duties to minors with multiple vulnerabilities.[16] Two PrEP studies[17,18] have faced these ethical complexities directly, and each generated new questions that must be answered to make progress toward providing minors' appropriate access to HIV prevention research. The first study, ATN 113, examined the safety and tolerability of oral TDF-FTC for minor YMSM. Concerns about disclosure-related vulnerabilities prompted study organizers to design the protocol to allow for adolescent self-consent so that parental permission was neither sought nor required for enrollment. ATN 113 was the first biomedical HIV prevention study in the U.S. that allowed minor adolescents to self-consent for enrollment however roughly half the study sites failed to secure IRB approval for protocol implementation.[19] The second study (MTN 023) is an active Phase IIa trial to assess the safety of a silicone vaginal ring impregnated with the antiviral dapivirine in adolescent women aged 15-17. Unlike ATN 113, MTN 023 study participants are required to have parental permission for enrollment. The study is underway, but investigators have encountered difficulty accruing participants within the planned timeframe for enrollment, raising concerns about the recruitment effects of requiring parental consent. Thus, neither of the two models of consent (adolescent self-consent or required parental permission with adolescent assent) facilitates adolescent inclusion in biomedical prevention trials. The first raises concern about exposure of the adolescent to harm; the second fails to attract adequate numbers because of the high risk for disclosure. Both raise important questions about the role of potential disclosure-related harms, participant gender, and study agent (delivery mechanism and stage of development) in shaping the consent process.

1.2 Rationale

This study will test a new model of consent for biomedical HIV prevention studies - optional parental permission. Consent has typically focused on a single actor--parent giving permission, or adolescent consenting for self. However, we will test a third model that includes the possibility of multiple actors. This support for a model of optional parental consent comes from a Phase III vaginal microbicide trial in South Africa.[20] Schenk et al. recruited 16-17 year-old girls and allowed them to self-consent for enrollment with the option to involve their parents if desired. The researchers were able to enroll and retain minors at very high risk of HIV, and found no differences in their attrition, adherence, or risk behaviors compared to 18-19-year-old study participants. These findings suggest that not only can minors participate in biomedical prevention studies but they can also be enrolled in a developmentally sensitive way. We want to determine whether a similar consent model would acceptable to high-risk adolescents and parents of high-risk adolescents in the US.

1.3 Preliminary Studies

Adolescents' capacity to consent to biomedical HIV research is roughly similar to that of adults. Ott has examined adolescent capacity to consent to research, and demonstrated that adolescents' capacity to understand consent information, to appreciate their own situation, the ability to balance risks and benefits, and to make a voluntary choice was similar to studies of adults.[21] These data are similar to that of Hein, et. al.[22] Through the Adolescent Medicine Trials Network ATN) for HIV/AIDS Interventions, Ott and Zimet examined preventive misconception with a simulated HIV vaccine trial. In that study (ATN 076), adolescents demonstrated the capacity to understand that the vaccine was an experiment (and thus may not work) and that a placebo would be used. Similar to adult studies and consistent with poor numeracy in U.S. populations, a higher number had difficulty understanding the statistical concept of randomization.[23]

Lewis-Gilbert, Knopf, Zimet, et al. evaluated the process of initiating ATN 113 across the 13 sites that intended to participate in the study. The study raised numerous ethical challenges that primarily revolved around the principle of respect for persons. Investigators and IRB members expressed concerns about adolescent vulnerability that were not resolved even when there was a legal basis for adolescent self-consent.[19] We also found that investigators and IRB members wished for an optional parental consent model, noting that some adolescents would want parental involvement in the consent process and some would not.[24] These studies point toward the acceptability of an optional parental consent model from the perspective of investigators and IRBs. The current study will elicit adolescent and parent perspectives.

2.0 SPECIFIC AIMS

The purpose of this study is to examine how the consent process affects the acceptability of participation in biomedical HIV prevention trials, from the perspective of behaviorally high-risk minors and the parents of minor adolescents. Acceptability will be measured by adolescents' willingness to participate (WTP) in and parents' willingness to support (WTS) their adolescent's participation in two hypothetical biomedical HIV prevention trials that are modeled after PrEP studies that included minors.

Aim 1: Describe how consent conditions influence high-risk minor adolescents' WTP in a hypothetical biomedical HIV prevention trial.

Primary Hypothesis: Adolescents assigned to the self-consent model will have the highest WTP scores, followed by those assigned to the adult permission model, and finally those assigned to the required parent permission consent model.

Additional sub-aims:

- Determine whether concern about HIV, capacity to consent, family context and sociodemographic characteristics moderate the relationship between consent condition and WTP scores.
- Describe high-risk minors' perceptions of the risks and benefits of parental consent, how they anticipate the different models of consent would influence their WTP in prevention trials, and whether shared-decision making between minors and parents is feasible.

Aim 2: Describe the acceptability of different consent conditions, from the parent perspective.

Primary Hypothesis: The parental permission required scenario will be the most acceptable to parents, followed by the adult permission model, and finally the adolescent self-consent model.

Additional sub-aims:

- Determine whether concern about HIV, capacity to consent, and sociodemographic characteristics moderate the relationship between consent condition and acceptability.
- Describe parents' attitudes toward the various consent models, their perceptions of the risks and benefits of each model, and their conceptualization of a shared decision making process for consent.

Aim 3: Describe the effects of the study agent (stage of development and method of delivery) on high-risk minor adolescents' WTP scores and parents' acceptability scores

Primary Hypothesis: WTP and acceptability scores will be higher for the study of an oral medication that is already FDA-approved for adults compared to study of a topical agent that is still under investigation.

Additional sub-aims:

- Describe perceived risks and benefits of each study design, and how adolescents and parents anticipate the study design would influence their WTP/WTS the hypothetical trial.

3.0 STUDY DESIGN

This study will use a quasi-experimental design to explore how the informed consent process affects the acceptability of biomedical HIV prevention trials, from the perspective of behaviorally high-risk minor adolescents and the parents of minor adolescents. All study participants will complete a computer assisted self-interview (CASI) that collects demographic, social, behavioral, and attitudinal measures. Adolescent participants will undergo a simulated consent process for each of two hypothetical studies based on their randomized consent condition (Appendix II). Parent Participants will will undergo a simulated consent process that mimics what their own adolescent would hear while consenting for each of the two hypothetical studies. After each hypothetical study, parent participants will complete a CASI with three vignettes that describe each of the three possible consent conditions. Parents will rate the acceptability of each vignette. The order of vignettes, and the order of the two hypothetical studies, is varied to reduce the possibility of ordering bias. Hypothetical Study 1, modeled after ATN 113, is an open-label study of oral TDF-FTC and hypothetical Study 2, modeled after HPTN 077, is a Phase IIa trial of an injectable HIV integrase inhibitor.

Eligible adolescent participants will complete a demographic questionnaire, then be lead by RS through a simulated study consent process for one of two hypothetical studies. The consent process will be consistent with their randomly assigned consent condition. After completing the simulated consent process, the adolescent will complete a CASI assessing adolescents' WTP and will work with RS to complete the UCSD Brief Assessment of Capacity to Consent (UBACC)[25]. The

simulated consent process and follow-up assessments will then be completed for the second hypothetical study. After the second UBACC, the adolescent will complete overall WTP, medical mistrust, and end of study questions.

Eligible parent participants will first complete a demographic questionnaire. They will then review the informed consent form for the first study with the RS and complete a CASI assessing the acceptability of three approaches to consent, presented in three different vignettes (please see section 3.4.2 for further information). Parents will work with RS to complete the UCSD Brief Assessment of Capacity to Consent (UBACC)[25]. The simulated consent process and follow-up assessments will then be completed for the second hypothetical study. After the second UBACC, the participant will answer a series of questions via CASI.

A subset of adolescent and parent participants will be selected to participate in a debriefing interview.

3.1 Study Population

This study will recruit adolescents between ages 14-17, inclusive, who are able to read and speak English, who have a negative or unknown HIV status; and who have engaged in high-risk sexual activity (see **Table 1**) in the last 12 months. The study will also recruit adults who are able to read and speak English, who are a parent or guardian to an adolescent who is between ages 14-17, inclusive, and who have a negative or unknown HIV status. Adolescent and parent participants will be recruited from four U.S. cities: Baltimore, MD; Chicago, IL; Denver, CO; and, Tampa, FL. These cities have diverse populations, high rates of incident HIV infection among adolescents and young adults, and/or demonstrated success in recruiting minor adolescents for biomedical HIV research. Recruitment will be primarily clinic-based, but if that method proves insufficient for recruiting participants, we will employ a variety of strategies for recruitment including: social media advertising, fliers, and word of mouth.

3.2 Sample Size

This study will enroll approximately 144 (36 per study site) high-risk minor adolescents and 144 (36 per study site) parents of adolescents. A subset of 24-32 (6-8 per study site) adolescents and 24-32 (6-8 per study site) parents will be selected to participate in the debriefing interview. Of note, the adolescents and parents will not be parent-child dyads; they will be unrelated. We project total enrollment of 288 participants, however, since this is a multi-site project with simultaneous recruitment with a hard to reach population, we may schedule and enroll more subjects than anticipated.

3.3 Study Randomization, Stratification, or Description of Non-Random Assignment Procedures

Adolescents will be randomized in a 1:1:1 ratio into 1 of the 3 consent conditions using block randomization with block size k=3 (so that in every 3 subjects, exactly 1 is allocated to each condition). The randomization will be stratified by study site and sex assigned at birth. Within study site, sex assigned at birth, and consent condition, the order in which the hypothetical trials will be presented to adolescents will be block randomized with block size k=2.

Enrollment of parents will be restricted to approximately 15 parents of adolescent natal males and 15 parents of natal adolescent females at each study site. Parents will indicate the acceptability of each of the three consent conditions for each of the two hypothetical trials. Independently of the gender strata, the order of hypothetical trial presentation will be block randomized with blocks size k=2. Separately for each hypothetical trial, the order of evaluation for the three consent conditions will be randomized so that each ordering is equally likely.

A subset of 6-8 adolescents (3-4 natal males and 3-4 natal females) and 6-8 parents of adolescents (3-4 parents of natal males and 3-4 parents of natal females) at each site will be selected for participation in the debriefing interview. All study participants will be asked if they are willing to participate in the debriefing interview until quotas have been reached.

3.4 Outcome Measures

3.4.1 Adolescents' Willingness to Participate (WTP) Scores

Adolescents' WTP will be used to measure the acceptability of biomedical HIV prevention trials from the perspective of high-risk minor adolescents. Adolescent WTP is measured using the question "If offered the chance, how likely would you be to participate in the study?" with response options ranging from "definitely not participate" to "definitely participate". The adolescent WTP will be measured after each of the two simulated study consent is completed, resulting in two WTP scores per adolescent.

3.4.2 Parents' Willingness to Support (WTS)

We use a number of measures to assess WTS a minor adolescent's participation in the study. The most obvious way to assess WTS is to ask the parent whether s/he would grant permission for his/her teenager to enroll in the study. However, this question can only be asked after the scenario in which parental permission is required because in the other two scenarios parental permission is either optional or not solicited, rendering the parent's preferences about participation moot. Thus, WTS includes not only projected likelihood of granting permission to join the study, but also: (1) a measure of the extent to which the parent finds the vignette's consent scenario an acceptable process for enrolling his/her adolescent; (2) measures of the parent's perception of his/her adolescent's capacity to consent to the two studies in question; (3) a measure of the parent's expectation that his/her adolescent would discuss the study prior to enrollment, even if such a discussion were not required; (4) a measure of the likelihood a parent would allow his/her adolescent to join the study. In summary, after each vignette the parent will answer two or three Likert-type questions that together will be used to assess WTS.

3.4.3 University of San Diego Brief Assessment of Capacity to Consent (UBACC) Scores

The UBACC will be administered to all participants. The UBACC includes ten open-ended questions to measure participant's understanding of research design, risks and benefits, and voluntariness. Each of the ten items are given a score of 0 indicating "a clearly incapable response", 1 indicating uncertainty or a partially appropriate, or 2 indicating "a clearly capable response". The UBACC will be completed for each of the two simulated studies, resulting in two UBACC scores per participant.

3.4.4 Qualitative Debriefing Interviews

The debriefing interview is a 30-45 minute interview designed to explore adolescent and parent perspectives on the various consent conditions in greater depth, and to better understand the role of study features, family, and adolescent characteristics in willingness to participate/willingness to support the hypothetical research studies. At the start of the interview, the participants will be informed that the interview will be recorded and transcribed and the participant will be asked to select a pseudonym for the researchers to use. The adolescent debriefing interview will consist of five sections including (1) general opinions about participating in HIV prevention studies, (2) opinions on the two specific studies, (3) relationship to parents, (4) opinions about parental involvement in the consent process, and (5) options/opinions for consenting in future studies. The parent debriefing interview will consist of four section including (1) general opinions about HIV prevention studies, (2) relationship to their teenager, (3) opinions about parental involvement in the consent process, and (4) options/opinions for consenting in future studies.

4.0 SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

4.1 Adolescent Inclusion Criteria

To be considered eligible for enrollment, an adolescent must meet all the criteria listed below.

4.1.1 Age 14-17 inclusive; and

4.1.2 Able to read and speak English; and

4.1.3 HIV status is negative or unknown; and

4.1.4 Engaged in high-risk sexual activity (**Table 1**) in the last 12 months; and

4.1.5 Not the child of a parent already enrolled in the study.

4.2 Parent Inclusion Criteria

To be considered eligible for enrollment, a parent must meet all the criteria listed below.

4.2.1 Able to read and speak English; and

4.2.2 Parent or guardian of an adolescent who is between ages 14-17; and

4.2.3 not the parent of a child already enrolled in the study.

Table 1. Criteria for high-risk sexual behavior

High-risk sexual behavior criteria for natal males	High-risk sexual behavior criteria for natal females
During the last 12 months, which of the following is true for you? (check all that apply): • I had unprotected anal sex with a male • I had protected anal sex with 3 or more males • I had sex with a male for money, gifts, shelter, or drugs	During the last 12 months, which of the following is true for you? (check all that apply): • I had unprotected anal or vaginal sex with a male • I had sex with someone who is HIV+ • I had protected vaginal or anal sex with 3 or more males

• I had sex with a male, and I have had a sexually transmitted infection (gonorrhea, chlamydia, syphilis, herpes) • I had sex with someone who is HIV+ • I had anal sex with a male and the condom slipped off or broke • None of the above	• I had sex with a male for money, gifts, shelter, or drugs • I have had sex with one or more males, and I have had a sexually transmitted infection (gonorrhea, chlamydia, syphilis, herpes) • I had vaginal or anal sex with a male and the condom slipped off or broke • None of the above

4.3 Recruitment and Screening

This study will recruit adolescents between ages 14-17, inclusive, and parents of adolescents in the same age range. Participants will be recruited from four partnering research sites in the following U.S. cities: Baltimore, MD (partnering organization: Johns Hopkins University, partnering researcher: R. Sanders), Chicago, IL, (partnering organization: University of Chicago, partnering researcher: J. Schneider), Denver, CO (partnering organization University of Colorado, partnering researcher: D. Reirden), and Tampa, FL (partnering organization University of South Florida, partnering researcher: D. Straub).

Specific recruitment procedures for each group are described in detail below.

4.3.1 Adolescents aged 14-17:

This study will recruit 36 adolescents at each site primarily through contact in the clinical setting. If recruitment is slow, we will begin using advertising on social media (Facebook, Twitter, chat services); support centers for lesbian, gay, bisexual, transgender, and questioning (LGBTQ) youth; churches and other social settings (e.g. Gay Straight Alliance at local high schools) and at clinics affiliated with the partnering organization. All interested adolescents will complete a screening questionnaire that should take about 10 minutes to complete. Adolescents recruited in person will complete the questionnaire on a tablet on the same day they are recruited. Adolescents who self-refer or hear about the study from friends will need to complete the screening questionnaire online. All eligible adolescents will provide contact information regardless of recruitment and screening method.

To avoid the accidental inclusion of parent-child dyads, we will ask each participant to give the first 5 digits of their street address and first 4 characters of apartment/unit, where applicable. For example, if someone lived at 1234 Main Street Apt. 408, the value for that address would be 01234408. The value will be labeled “Family ID” and stored only until the end of the enrollment period. Once the site has filled all quotas, the Family ID will be permanently deleted. The RS will receive an email from Qualtrics indicating the participant’s eligibility. If the participant is eligible based on the screening questionnaire, the RS will use the Family ID Report in Qualtrics to idenfity any matching Family IDs. If there is no match, the participant qualifies and can begin the study. All eligibility requirements are assessed without the PI’s input. If interested, the adolescent will either: 1) provide contact information to arrange the study visit or 2) complete the study procedures the same day as s/he was screened. Eligible participants will be invited to participate in an on-site debriefing interview (until quota is filled), immediately following the final CASI.

4.3.2 Parents or guardians:

This study will recruit 36 parents/guardians at each site. Parents will be recruited primarily through contact in the clinical setting. If recruitment is slow, we will begin using advertising on social media (Facebook, Twitter), the LGBTQ youth centers referenced above, and through the local chapters of Parents, Families, and Friends of Lesbians and Gays, as well as churches, and other social settings familiar to our target audience. Parents recruited in person will complete the questionnaire on a tablet on the same day they are recruited. Parents who self-refer or hear about the study from friends will need to complete the screening questionnaire online.

To avoid the accidental inclusion of parent-child dyads, we will ask each participant to give the first 5 digits of their street address and first 4 characters of apartment/unit, where applicable. For example, if someone lived at 1234 Main Street Apt. 408, the value for that address would be 01234408. The value will be labeled "Family ID" and stored only until the end of the enrollment period. Once the site has filled all quotas, the Family ID will be permanently deleted. The RS will receive an email from Qualtrics indicating the participant's eligibility. If the participant is eligible based on the screening questionnaire, the RS will use the Family ID report in Qualtrics to identify any matching Family IDs. If there is no match, the participant qualifies and can begin the study. All eligibility requirements are assessed without the PI's input. If interested, the parent participant will either: 1) provide contact information to arrange the study visit or 2) complete the study procedures the same day as s/he was screened. Eligible participants will be invited to participate in an on-site debriefing interview (until quota is filled), immediately following the final CASI.

4.4 Locator/Contact Information

At the end of the screening questionnaire, interested and eligible individuals will be asked to provide their preferred method of contact and an alternative method of contact. A method of contact may be an email address, phone number, or Facebook profile name. Participants will review a sample voice/text message, and then asked if such messages can be sent (via SMS) and/or left (voicemail) via their preferred contact information. RS will only send/leave messages if expressly permitted to do so. Contact information will be accessible by designated research staff at the relevant research site, as well as the data manager, Program Manager, and the PI. All contact information will be stored in the "Scheduling Log", which is separated from the study visit data. IU researchers will have access to the scheduling log for monitoring purposes.

4.5 Informed Consent

After a screened participant is determined to be eligible, s/he will receive a study information sheet and provide verbal consent for the study. The study details will be discussed and all questions answered during the informed consent process. Written consent is not required, since this would include the only identifying information for participants in the study. Minors will not require parental consent to participate. Verbal informed consent from the individuals as determined by local Institutional Review Boards (IRB) will be obtained before any study related procedures are performed. Enrollment will occur after participant consent is obtained.

Those individuals who refuse to provide verbal consent to participate in the study will be asked if they are willing to provide their reason for declining participation and if answered; the responses will be recorded in an anonymous manner on the screening questionnaire.

4.6 Co-enrollment Guidelines

Co-enrollment in other clinical studies is allowed and approval from the Protocol Team for co-enrollment is not required.

5.0 STUDY PROCEDURES

A Schedule of Evaluations, located in Appendix 1, provides a timeline for each study activity.

5.1 Enrollment Procedures

Enrollment and study completion will occur on the same visit. Participants who are confirmed eligible and complete the consent process will immediately begin the study procedures. The participant will be considered enrolled after they provide verbal consent.

5.2 Randomization Procedures

5.2.1. Adolescent Participants

Adolescents will be randomized in a 1:1:1 ratio into 1 of the 3 consent conditions using block randomization with block size k=3 (so that in every 3 subjects, exactly 1 is allocated to each condition). The randomization will be stratified by study site and sex assigned at birth. Within study site, sex assigned at birth, and consent condition, the order in which the hypothetical trials will be presented to adolescents will be block randomized with block size k=2.

A subset of 6-8 adolescents (3-4 of both sexes) at each site will be selected using quota sampling for participation in the debriefing interview. Participants will be asked if they are willing to participate in the debriefing interview unless the quota for their demographic group has been reached.

5.2.2. Parent Participants

Enrollment of parents will be restricted to approximately 18 parents of adolescent natal males and 18 parents of natal adolescent females at each study site. Parents will indicate the acceptability of each of the three consent conditions for each of the two hypothetical trials. Independently of the gender strata, the order of hypothetical trial presentation will be block randomized with blocks size k=2. Separately for each hypothetical trial, the order of evaluation for the three consent conditions will be randomized so that each ordering is equally likely.

A subset of 6-8 parents at each site will be selected using quota sampling for participation in the debriefing interview. Participants will be asked if they are willing to participate in the debriefing interview unless the quota for their demographic group has been reached.

5.3 Investigation Procedures

RS will prepare the participant's iPad for the beginning of the study visit. Adolescents will complete demographic, social, and attitudinal measures by CASI. Once completed, RS will begin

the simulated consent process for study 1 or study 2 (depending on randomization) by reviewing the hypothetical consent form (which reflects the randomly assigned consent condition; Appendix II). RS will allow time for questions about the hypothetical study from the participant, provide answers as needed. The RS will then ask the adolescent to complete the WTP questions on their iPad. Finally, the RS will administer the UCSD Brief Assessment of Capacity to Consent (UBACC)[25] for study 1 or study 2 (depending on randomization). The RS will then repeat the simulated consent process, WTP, and UBACC for the additional hypothetical study (study 1 or study 2 depending on randomization).

For parent participants, RS will prepare the participant's iPad for the beginning of the study visit. RS will begin the simulated consent process for study 1 or study 2 (depending on randomization) by reviewing the hypothetical consent form (which reflects the randomly assigned consent condition; Appendix II). RS will allow time for questions about the hypothetical study from the participant, provide answers as needed. The RS will then ask the parent to read the vignettes and answer WTS questions on their iPad. Finally, the RS will administer the UCSD Brief Assessment of Capacity to Consent (UBACC)[25] for study 1 or study 2 (depending on randomization). The RS will then repeat the simulated consent process, vignettes and answer WTS questions, and UBACC for the last hypothetical study (study 1 or study 2 depending on randomization). Parents will then complete demographic, social, and attitudinal measures by CASI.

For both adolescent and parent participants, after all data are collected and saved, the RS will determine whether the participant is eligible to participate in the debriefing interview. Eligibility is determined by quota (3-4 natal male adolescents and 3-4 natal female adolescents at each site; 3-4 parents of adolescent natal males and 3-4 parents of adolescent natal females at each site). If the quota is not filled, the participant will answer a question at the end of the Qualtrics survey asking if they would like to participate in a debriefing intertivew. If quota is filled, the RS for that site will be notified and IU will remove the question from Qualtrics.

The participants will complete all CASIs using Qualtrics database via a provided iPad.

The RS will verbally administer the UBACCs. UBACCs and debriefing interviews will be audio recorded with participants permission.

5.4 RS Training

Interview RS training, intervention monitoring, and quality control (section 5.5) will be done by Dr. Knopf and the Consent 2.0 Program Manager. RS conducting the interviews will ideally have some experience with open-ended questioning and interviewing (e.g., HIV counseling, anthropology, psychology, nursing, social work); however, experience is not absolutely necessary, and an individual with good listening and interpersonal skills can be trained in the technique.

Dr. Knopf will visit each research site to conduct initial RS training over the course of two days. The two day training will cover:

- Background and rationale for project
- Project goals

- Work with human subjects, with special attention to issues of adolescent consent to biomedical HIV prevention research
- Overview of the two hypothetical research studies
- Overview of all study instruments
- Practice interviewing, using actual study instruments
- Debriefing of practice interviews to identify areas of improvement
- Writing field notes
- Dealing with participant disclosures
- Directed reading on qualitative techniques

Practice interviews will focus on self-presentation, and specific interview techniques, such as active listening, use of silence, avoiding leading questions, outlining, summarizing, and tabling (when the adolescent participant brings up two interesting concepts, tabling one and pursuing the other).

5.5 Monitoring/Quality Control

Monitoring and quality control for the debriefing interviews will be done by a qualitative research team consisting of Dr. Knopf and the Consent 2.0 Program Manager.

Quality of CASI and debriefing interviews will be intensely monitored at the start, and then periodically by the qualitative research team. After each of the first three interviews at each site, and before the fourth interview takes place, the qualitative research team will listen to the interview. Together, they will discuss the interview, covering (1) interview technique (good and bad), (2) interview content, (3) techniques to practice in the next interview, and (4) areas for further inquiry.

After listening to the first several together, a subset of subsequent interviews will be listened to by the qualitative research team. These will be identified by either the RS or the qualitative research team, and include interviews that went particularly well or particularly poorly, or interviews with interesting content.

6.0 EVALUATIONS AND MEASURES

6.1 Screening

All interested adolescents and parents/guardians will complete a screening questionnaire either in person on a study tablet, or online on the interested person's personal computing device (desktop, tablet, smartphone).The survey software will automatically determine whether the individual meets the eligibility requirements without the PI's input.

6.2 Enrollment/Entry

RS will prepare the participant to complete demographic, social, and attitudinal measures by CASI. Adolescent participants will complete these measures in two parts. The beginning CASI will include demographic information, SES, parental monitoring, and concern about HIV and the final CASI will include overall WTP, medical mistrust, and closing questions. Parent participants

will complete demographics, SES, WTS, concern about HIV, medical mistrust, and closing questions during the final CASI. The measures are summarized in **Table 2**, below.

6.2.1 Quantitative Evaluations

Table 2: Quantitative Measures

Demographics	Scale	Description of Items included
Demographics		Age, race/ethnicity, sexual orientation, gender identity, education, employment, health insurance status, city, living situation
Socioeconomic Status	FAS-III [26 27] (Adolescents)	7- questions adapted from the Family Affluence Scale-III, measuring a family's financial status based off of number of vehicles, computers, bathrooms, adolescent having their own bedroom, if the family has a dishwasher, number of times traveled outside US, and overall perception of family's financial status.
Social Support	MSPSS- modified[28]	4 –Likert questions on a 7-point scale ranging from very strongly disagree to very strongly agree, measuring parental support and relationships with adolescents.
Parental Monitoring	Parental knowledge - modified[29] (Adolescents & Parents)	5- point Likert scale measuring parental knowledge, disclosure, solicitation, and parental control. The scale has 25 statements for the (adolescent/parent) Strongly Disagree to Strongly Agree for each statement. Adolescent statements such as "My parent(s) know what I do during my free time. Parent statements such as "I know what my teen does during his/her free time."
Medical Mistrust[30]	(Adolescents & Parents)	6, 5-point Likert items that measure the degree to which the participant trusts medical researchers.
Communication	Communication with Parents[31] (Adolescents & Parents)	5 Questions asking the number of times parents and adolescents have communicated about relationships, sex, sexually transmitted infections (HPV, HIV), same sex relationships, and using a condom. Answers range from Never, Once/twice, Many times, and Don't know
Concern about HIV	HIV Risk perception[32] Adolescents & Parents	2, 5-point Likert questions about adolescent worry of being infected with HIV/AIDS and parents worry of their adolescent being infected with HIV/AIDS.
Sexual Behavior	Sexual Behavior[33] (Adolescents)	5 questions for adolescents regarding sexual intercourse partners.
Capacity to Consent	UBACC[25]	8 open-ended questions (answers scored 0-2) to measure participant's understanding of research design, risks & benefits, voluntariness
Acceptability	Willingness to Participate[33] (Adolescents)	3 Likert-type items that begin with question stems such as "If offered a chance to participate in this study, how likely are you to participate…"

	Acceptability of consent approach Assessment of adolescent capacity to consent Confidence in adolescent disclosure (Parents)	Likert-type items (scored 1-5) that measure each of the three constructs.

6.2.2 Qualitative Evaluations

The debriefing interview is designed to explore adolescent and parent perspectives on the various consent conditions in greater depth, and to better understand the role of study features, family, and adolescent characteristics in willingness to participate/willingness to support the hypothetical research studies. At the start of the interview, the participants will be informed that the interview will be recorded and transcribed and the participant will be asked to select a pseudonym for the researchers to use. The adolescent debriefing interview will consist of five sections including (1) general opinions about participating in HIV prevention studies, (2) opinions on the two specific studies, (3) relationship to parents, (4) opinions about parental involvement in the consent process, and (5) options/opinions for consenting in future studies. The parent debriefing interview will consist of four sections including (1) general opinions about HIV prevention studies, (2) relationship to their teenager, (3) opinions about parental involvement in the consent process, and (4) options/opinions for consenting in future studies.

6.3 Premature Discontinuation from Intervention

The RS will complete the ATN 150 Off Study Form (located at the end of the Qualtrics RA survey) when the decision is made to permanently discontinue the subject from the study and no further data collection will occur. (See Section 8.4)

7.0 DATA COLLECTION AND SITE MONITORING

7.1 Development of Protocol and Case Report Forms

The ATN CC, in collaboration with the Protocol Team, is responsible for the development of this protocol and ATN regulatory forms (e.g. off Study form, untoward event form). Indiana University (IU) is responsible for constructing, testing, and implementing the CRFs and CASIs in Qualtrics. IU is also responsible for all qualitative data (from UBACC and debriefing interviews) for this study.

7.2 Data Records

Participant-related study information will be identified through the Study Identification Number (SID) on all participant CRFs, audiotapes, and CASI data. Participant names or other personally-identifying information will not be used on study documents with the exception of preferred name or nick name to be used during the interview, and contact information, such as email address, phone/text number, and/or Facebook profile, which is collected from eligible and interested participants. Contact information is used to schedule a time to complete the study visit.

Electronic CRFs and CASIs are completed and keyed directly into Qualtrics. Any printed study-related information will be kept in double-locked, limited access areas at the study sites.

7.3 Data Collection

7.3.1 Screening

Adolescents and parents of adolescents will be screened either online or in-person using CASIs developed in Qualtrics. Information regarding their eligibility for the study will be collected, along with the first 5 digits of their street address and first 4 characters of apartment/unit, where applicable, in order to rule out dyads. Eligible individuals will also be asked for basic contact information (see section 7.2).

7.3.2 Computer Assisted Self-Interview

Demographic, social, behavioral, and attitudinal measures will be collected using CASI developed within Qualtrics. The CASI responses will remain confidential; no personal identifying information will be collected. Detailed instructions regarding completion of the CASIs will be provided in site MOPs.

7.3.2.1 CASI Data Security

The CASI data will be collected on iPad devices using Qualtrics. Qualtrics is a web-based system appropriate for use with sensitive data, including those data protected by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data are stored on secure servers and protected by fire walls. No data is written to the iPad hard drive.

7.3.3 Audio Data for UBACC and Debriefing Interviews

The entire study visit, including UBACCs and debriefing interviews, will be digitally audio-recorded with participant consent. Immediately upon completion, the digital audio files will be uploaded to the Indiana University (IU) secure server. The audio recordings will be uploaded to a secure website belonging to a transcription company, who will listen to the recordings, transcribe them into a Microsoft Word file, and upload the transcript files to their secure website for download by IU study staff. Transcripts will be checked against audio recordings for accuracy. Once that process is complete, the audio files will be destroyed. Dr. Knopf will ensure that the audio files are destroyed by the transcription company, and permanently deleted from the IU server.

7.3.4 Electronic Case Report Forms

Data regarding study completion/early termination and protocol deviations will be collected using eCRFs developed within Qualtrics. The eCRFs will remain confidential; no personal identifying information will be collected. eCRFs will have the participants ATN Study ID number associated with the answers. Detailed completion guidelines for the eCRFs will be provided in the MOP.

7.4 Data Submission

All CASI and CRF data will be collected in electronic format using Qualtrics. For both the UBACC administration and debriefing interview data, the digital audio files will be uploaded to the IU

secure server. Then IU study staff will upload the digital audio files to a secure website belonging to a transcription company, who will listen to the recordings, transcribe them into a Microsoft Word file, and upload the transcript files to their secure website for download by IU study staff.

All data will be submitted to the NICHD's Data and Specimen Hub (DASH) after completion of the study in accordance with the NICHD DASH Data Archive Policy (https://dash.nichd.nih.gov/Resource/Policies) and the NIH Grants Policy Statement (https://grants.nih.gov/grants/policy/nihgps/HTML5/introduction.htm).

7.5 Data Quality Assurance

Investigators receiving federal funding must adhere to the Code of Federal Regulations (CFR) to protect research participants and produce reliable study information. Sites participating in research sponsored by the NICHD need to have an internal quality assurance (QA) plan that will identify problems and correct errors in research study records.

For debriefing interviews, data quality will be checked at two time points. Two team members will listen to segments of each debriefing interview digital recording for recording quality and completeness and each transcription will be checked against the debriefing interview digital recording for accuracy and completeness.

7.6 Role of Data Management

Indiana University is responsible for all eCRFs and CASI administration as well as data collection and cleaning. The IU Data Managerwill assist in protocol development and data analysis. The IU Data Manager will regularly receive data transfers from the Qualtrics database system for the purposes of producing study monitoring reports and/or to perform data analyses described in the statistical analysis plan or approved publication requests. Any data issues discovered by the DM will be reported to the PI and corrected in the Qualtrics database.

7.7 Study Site Monitoring and Record Availability

Site monitors from the CC will visit participating study sites to review compliance with the protocol, as well as accuracy and completeness of relevant study documentation and records, such as training logs. Regulatory files, as required, will also be inspected to ensure that regulatory requirements are being followed. Each site will work with the monitors to arrange a monitoring visit to ensure appropriate RS are available and that all documentation is accessible. Internet access will be required as well as appropriate space for the monitor to work.

Activities that may be performed and documents that may be reviewed by the monitor include review of study procedure and documentation regarding compliance with protocol, GCP, and regulatory requirements.

At the end of the monitoring visit, the monitor will meet with the PI, the study coordinator, and any other relevant RS to go over the findings.

7.8 Study Monitoring

Implementation of the study will be monitored by the Study Team Review Committee (STRC), which includes the Protocol Chair, NICHD Health Science Administrator, one co-Investigator, Consent 2.0 Program Manager, and the IU Data Manager.

7.8.1 Monitoring by Study Team Review Committee (STRC)

The STRC will meet at least monthly. During these meetings, the STRC will review enrollment reports, reports on early discontinuation of the one-day study visit, and reports on Untoward Events (UEs) that have occurred since the last STRC meeting or previously reported UEs for which new information is available. All UEs will be reviewed within one week of occurrence; if the next scheduled STRC meeting is more than 7 days after a UE occurred, the team will convene a special meeting to address it.

In the event that an UE occurs at a research site, the STRC will invite the relevant Site PI to attend either the regular STRC meeting or a specially convened meeting (see next section). During the STRC meeting the UE will be reviewed and the team will determine what actions are necessary. The Site PIs for Consent 2.0 will not be standing members of the STRC.

8.0 PARTICIPANT MANAGEMENT

8.1 Study Visit Management

This project requires one study visit. There are no follow up visits.

If an eligible participant does not show for a scheduled study visit, the RS will follow up and make at least three attempts to reschedule. Similarly, RS will make at least three attempts to contact all participants who are eligible and interested but unable to complete the study visit on the same day as screening questionnaire. Participants will be considered off study due to loss to follow up if they fail to respond or attend the study visit after the three attempts at contact/rescheduling.

8.2 Compensation

All participants will receive $50, in cash or gift card to compensate for their time. An additional $25 will be provided to participants who complete the debriefing interview. Each site will determine the most appropriate form of compensation. Gift cards may be: a Visa card, gas card, card for specific local store [e.g. Target, Wal-Mart]. In addition, sites may offer reimbursement for transportation. Each site will determine the most appropriate form of transportation reimbursement (e.g. bus fare, subway tokens, taxi vouchers, or cash). Participants who make a separate or unnecessary trip to the study site for screening but are deemed ineligible for any reason—including lack of interest—will receive $10 (cash or gift cards) as well as $5 transportation reimbursement (e.g. bus pass). These incentives will be available to any participant who screen fails until online screening has been established. After online screening has been established, RS may provide these incentives on a case by case basis at their discretion (e.g. in case someone cannot screen online and needs to come to the study site to

screen) Participants will receive $50 if they only stayed for part of the study visit. Participants will not receive any compensation for completing the online screening questionnaire.

8.3 Intervening on "Social Harms"

All sites have specific policies governing the treatment of human subjects. These policies specify that medical and psychological assistance will be available in the immediate environment in the event a participant should experience any adverse reactions resulting from study procedures.

While participants will be informed that they may refuse to answer any question at any time, responses or reactions to certain questions may indicate distress on the part of the participants. If at any time during the study, a participant divulges that he or she is at risk for harm, including but not limited to being abused or experiencing violence, if harm is suspected or likely, or if the participant states he or she is suicidal/homicidal, measures will be taken to ensure his or her safety. Reporting will be done as appropriate to the situation and the legal statutes, including reporting to child protection agencies or other appropriate agencies and referrals will be provided to appropriate support, counseling or treatment resources.

8.4 Criteria for Premature Discontinuation

Study participants will only complete one study visit. No participant follow up will be conducted; therefore premature study discontinuation will be limited to the following reasons:

8.4.1 Consent or assent withdrawn during CASI or interview;

8.4.2 Development of an untoward effect that warrants discontinuation from study; or

8.4.3 Failure to adhere to or complete study evaluations;

If it becomes apparent that a participant is becoming increasingly distressed while participating in any part of the study, the individual will be assessed by the RS (or designee) to determine whether they will be able to complete the session without experiencing undue distress. If the participant appears unable or refuses to continue participation, they will be offered a list of referral sources.

9.0 MONITORING UNTOWARD EFFECTS ASSOCIATED WITH OR RESULTING FROM STUDY

RS must follow the sIRB's procedure for reporting and managing untoward events (UEs). ATN protocols follow the ATN Manual of Policies and Procedures (MOPP) for UE reporting. The ATN Query Notification System (QNS) will be used to document the occurrence of an UE, as well as to provide the details, grading and rating of related or unrelatedness to the study. Protocol team members are notified through the ATN QNS.

9.1 Untoward Events Reporting

RS will enter any UE of grade 3 or above in the ATN QNS (https://www2.cscc.unc.edu/atn/node/add/untoward-event-150) within 48 hours of site awareness. Other events (Grades 1 and 2) will be expected to be entered in the ATN QNS within 7 days of site awareness of the untoward event.

All reported events will receive a grade by the RS. The grades are defined as noted below. The functional table below should be used to grade the severity of an UE. In addition, all deaths related to the study are to be classified as **grade 5**.

Table 3: Untoward events grading

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING	GRADE 5 DEATH
Event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death	Death
Examples	Discomfort over survey questions that were self-resolved or resolved without team intervention	Mild to moderate distress observed by study team resolved with team intervention.	Severe emotional distress observed by study team requiring evaluation or intervention.	Suicidal ideation or suicide attempt while on study.	Death

Adapted from https://rsc.tech-res.com/docs/default-source/safety/daids-ae-grading-table-mar2017.pdf?sfvrsn=6

The Study Team Review Committee (STRC), listed above in Section 7.8, are responsible for systematically reviewing all new UEs on regularly scheduled conference calls.

The Coordinating Center (CC) is responsible for presenting a cumulative report of all UEs reported in the ATN QNS for ATN 150. All UEs will be reviewed within one week of occurence;

if the next scheduled STRC meeting is more than 7 days after a UE occurred, the team will convene a special meeting to address it.

When an UE occurs at a research site, the STRC will invite the relevant Site PI to attend either the regular STRC meeting or a specially convened meeting. During the STRC meeting the UE will be reviewed and the team will determine what actions are necessary. The Site PIs for Consent 2.0 will not be standing members of the STRC.

The CC will follow required reporting procedures and related timelines. RS must also follow the sIRB's procedure for reporting these untoward events. For any events where it is learned that community members or RS members experience negative events associated with the study, the event will be reported to the STRC for review and determination of outcomes.

9.2 Reportable Events by Populations

There are three types of untoward events to be identified: (1) those related to the participating adolescent or parent, (2) those related to the RS, (3) those related to the community.

First, the study will catalogue any untoward event experienced by the participant that may be attributable to participation in or the conduct of the study. Reporting is required for occurrences including social harms and psychological distress, and serious life-threatening events such as suicide attempts. These may be immediately apparent to the RS, such as the participant's emotional upset requiring referral for counseling; or they may be delayed and reported later to R, such as physical harm to a participant for having participated in the study.

Second, RS may encounter untoward events during the conduct of this study that personally affect them. Training and guidance will seek to minimize this risk. Nonetheless, an assessment of the cost of conducting this study must include cataloguing these events as well. The Protocol Team should be notified of these events using the ATN QNS so that they may be immediately addressed, evaluated, and guidance modified or expanded to minimize similar risk to other staff.

Third, the community may also be affected by an UE. Examples of community level UEs include any adverse community feedback received by the research institution or team concerning the study and the study being portrayed adversely in any community forum or in the media. RS will also report any UEs that affect the community in the ATN QNS. Both staff and community level untoward events do not receive a grade.

10.0 STATISTICAL AND ANALYTIC CONSIDERATIONS

10.1 Study Design

This study will use a quasi-experimental design to explore how the informed consent process affects the acceptability of biomedical HIV prevention trials, from the perspective of behaviorally high-risk minor adolescents and the parents of minor adolescents.

Adolescent participants will undergo a simulated consent process for each of two hypothetical studies based on their randomized consent condition. Hypothetical Study 1, modeled after ATN 113, is an open-label study of oral TDF-FTC and hypothetical Study 2, modeled after HPTN 077,

is a Phase IIa trial of an injectable HIV integrase inhibitor. After completing the simulated consent process for the first hypothetical study, the adolescent will complete a CASI assessing the adolescents' WTP and will work with RS to complete the UCSD Brief Assessment of Capacity to Consent (UBACC).[28] The simulated consent process and follow-up assessments will then be completed for the second hypothetical study. The presentation order for the two hypothetical studies will be randomly determined (see Section 3.3 for more details on the randomization procedure).

Parent participants will review all three consent conditions for each of the two hypothetical studies and complete a CASI assessing the acceptability of the three approaches to consent. The presentation order of the hypothetical studies and the review order for the consent conditions for each hypothetical study will be randomly determined (see Section 3.3. for more details on the randomization procedure).

10.2 Study Endpoints

There are primary key endpoints for this study:

1. Adolescent WTP scores (values 1 through 5) converted from a Likert scale (definitely not participate, probably not participate, might or might not participate, probably participate, definitely participate). Adolescent WTP scores are the measured adolescent response to the question: "If offered the chance, how likely would you be to participate in the first/second study?"
2. Parental WTS scores are the measured parent response to three vignettes. Parents are asked the same vignettes after listening to Study 1 and Study 2. The vignettes and study orders are varied.
    a. Vignette 1 states: "Imagine your teen wants to join the study we just described. Your teen asks you to come to the research clinic with them. You are given information about the study, and have the opportunity to ask any questions you want to ask. After your questions are answered, you are asked to give your permission for your teen to join the study. In this approach to consent, you have the final say about whether your teen can join the study. How acceptable is this approach to research consent?"
    b. Vignette 2 states: "Imagine your teen wants to join the study we just described. Your teen comes to the research clinic on their own. They read the consent form, and have an opportunity to ask questions. Your teen is required to have an adult's permission to sign up for the study. They can choose to ask either you or a neutral adult, called an "ombudsman." The ombudsman is not in charge of the study; the ombudsman's job is to ensure your teen understands the research study, and to help your teen think about the risks and benefits of joining the study. Your teen would need either your permission OR the ombudsman's permission to join the study. In this approach to consent, your teen must have an adult's permission to join the study; your teen would be able to choose whether to seek permission from you or the ombudsman. How acceptable is this approach to research consent?"

c. Vignette 3 states: "Imagine your teen wants to join the study we just described. Your teen comes to the research clinic on their own. They read the consent form, and have an opportunity to ask questions. Once their questions are answered, your teen is ready to consent to the study. They are allowed to sign the consent form without speaking to anyone else about the decision. In this approach to consent, your teen is allowed to make the decision about joining the research study on their own. How acceptable is this approach to research consent?

The vignette responses are based on a 5-point Likert scale with values ranging from 'completely unacceptable' to 'completely acceptable.'

Of note, more comprehensive data are collected regarding parental WTS for the three consent conditions, including: (1) measures of the parent's perception of his/her adolescent's capacity to consent to the two studies in question and (2) a measure of the parent's expectation that his/her teen would discuss the study prior to enrollment, even if such a discussion were not required. Since these measures are not applicable to all consent conditions, they were not used in the definition of the primary endpoint.

10.3 Sample Size and Power Estimates

This study is powered to detect a meaningful difference in adolescent WTP scores and to detect a meaningful difference in parental WTS scores between the three consent conditions being studied. The WTP scores will be estimated as the mean score of three 5-point Likert scales. Based on the assumption that adolescent WTP scores are normally distributed and analyses using a linear regression model based on 120 participants (40 per consent condition) and with 7 independent variables in the model will provide 80% power to detect a 0.09 f^2 effect size, which is between a small (f^2=0.02) and a medium effect size (f^2=0.15), for consent conditions. This power calculation, which assumed a single observation per participant, is conservative and the actual study which will have two observations per participant (one for each simulated consent process) will have a larger statistical power to detect an f^2=0.09 effect size for consent condition. Since the test of consent condition effects based on parental WTS scores is a within-participant comparison rather than an across-participant comparison, a test of parental consent condition effects will have 80% power to detect an even smaller effect size (f^2) compared to tests for consent condition effects using adolescent WTP scores.

A subset of 24–32 (6–8 per study site) adolescents and 24–32 (6–8 per study site) parent participants will be selected to participate in the debriefing interview. Prior research with similar populations suggest that this sample size is sufficient for eliciting a variety of perspectives and establishing key themes in the data.

10.4 Statistical Analysis Plan

10.4.1 Quantitative Data Analysis

The primary analyses will estimate the effect of the three conditions and two hypothetical trial types on adolescent WTP scores and parent WTS scores. All analyses will be performed separately for adolescents and parents. The type I error rate will be set to $\alpha = 0.05$ separately for adolescent-specific and parent-specific hypothesis tests.

Linear mixed models will be used to estimate the effect of the three consent conditions and two trial types on WTP and WTS scores, with a random participant effect (i.e. random intercept) to account for the potential correlation between the multiple responses per participant. Aside from consent condition and trial type effects, the LMMs will also include adolescent's sex assigned at birth and study site as fixed effects.

Heterogeneity of consent condition and trial type effects across study sites will be evaluated. If statistically significant interactions occur ($p<0.05$), site-specific estimates of effects will be presented to supplement the pre-planned analyses. P-values from pairwise comparisons of consent condition effects will be adjusted for multiple comparisons to control the type I error rate at the level $\alpha=0.05$ separately for parents and adolescents. Tests of trial type effects will be performed at the level $\alpha=0.05$ separately for adolescents and parents and separately from tests of consent condition effects.

As a secondary sensitivity analysis, we will evaluate whether concern about HIV, family context (frequency of communication, connectedness), and other demographic and socioeconomic factors affect WTP/WTS participation in biomedical research. We will examine these effects by adding variables into the models to determine if they moderate the relationship between consent condition and WTP/WTS scores.

Although WTS and WTP scores are discrete, it is common to analyze these data using linear models. Research suggests that this approach is robust to the discrete nature of the data if the normality assumption is not severely violated. However, usage of the LMM may be problematic if a large number of responses occur on the boundary (e.g. a high proportion of 1's or 5's). In this case we will fit a linear quantile mixed model for the median WTP and WTS scores, which does not require normality.[34]

The primary endpoint analyses will be based on the observed data. By study design requirement, it will not be possible for sex assigned a birth to be missing and so no methods for missing covariates are needed for the primary analyses. If a key demographic or socioeconomic measures are missing in more than 5% of participants, the secondary sensitivity analyses described above will utilize multiple imputation by chained equations for those analyses.[35]

The effect of the three conditions on the mean adolescent UBACC scores will be estimated using linear mixed-effect models (LMMs) that include a random participant effect (i.e. random intercept) to account for correlation between the multiple UBACC assessments per participant. Aside from consent condition and trial type effects, the LMMs will also include adolescent's sex assigned at birth and study site as fixed effects.

The effect of the trial type on the mean parent UBACC scores will be estimated using LMMs that includes a random participant effect (i.e. random intercept) to account for correlation between the multiple UBACC assessments per participant. Aside from trial type effects, the LMMs will also include adolescent's sex assigned at birth and study site as fixed effects.

Using the same strategy described in Section 6.1 (e.g., to evaluate how demographic factors affect WTP/WTS participation), we will perform analyses that evaluate the extent to which capacity to consent, as measured by the UBACC, influences WTP/WTS scores.

10.4.2 Qualitative Data Analysis

Our analytic approach to the qualitative data collected during de-briefing interviews is qualitative description, as described by Sandelowski.[36] Qualitative descriptive methods provide an in-depth description of experiences shared by a group facing a common challenge and are particularly useful for generating summaries of information to guide future interventions. The PI will analyze the transcripts using conventional content analysis techniques as described by Hsieh & Shannon.[37] Each text unit (meaningful phrase, sentence, or story relevant to the study aims) will be extracted and coded with a short phrase that reflects its essence. A case-ordered meta-matrix[38] will be constructed, with each row representing an individual and each column representing variables (from quantitative measures) and constructs (from the interviews) of interest. Separate matrices will be made for adolescents and parents, for ease of comparison. The research team will categorize all the codes in each column and provide a description of each category to describe the variable fully from the parents' and YMSM perspective. For example, all the codes under barriers to parental involvement will be categorized to provide a list of barriers, and the barriers identified by each group will be compared to consider differences in the two groups' perspectives. An example data matrix is shown in **Table 4**.

Table 4: Sample qualitative data analysis matrix for adolescent participants

Participant ID	Demographic Data				UBACC	Qual Interview Constructs					
	Age	Gender Identity	Education	Living Situation	Willingness to participate	Relationship to parent	Relationship to parent	Willingness to involve a parent	Barriers to parent involvement	Facilitators of parent involvement	Concerns about protocol
NNNNNN											
NNNNNN											
NNNNNN											

10.5 Missing, Unused and Spurious Data

Every effort will be made to ensure that the amount of missing data is kept to a minimum as missing data complicates the statistical analyses or results in biased parameter estimates. The primary analyses will be based on the observed data. As a sensitivity analysis, to be performed if more than 5% of adolescent WTP scores and/or 5% of parental WTS scores are missing, we will perform a multiple imputation analyses using the method of chained equations[39] to evaluate the impact of non-response on the primary analyses. By study design requirement, it will not be possible for sex assigned a birth to be missing in this study and so no methods for missing covariates are needed for the primary analyses. If a key demographic or socioeconomic

measure is missing in more than 5% of participants, the sensitivity analyses described in Section 10.4.1 will utilize multiple imputation by chained equations.

11.0 HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, ICH Good Clinical Practice guidelines, and 45 CFR Part 46.

11.1 Participants' Confidentiality

Potentially identifying information is given in the screening form, and used for determining eligibility and scheduling the study visit. To be eligible, a screened participant cannot share a home with an enrolled participant. Thus, as stated in sections *4.3.1* and *4.3.2*, participants will input the first 5 digits of their street address and first 4 characters of their apartment/unit, when applicable. For example, if someone lived at 1234 Main Street Apt. 408, the value for that address would be 01234408. The value will be labeled "Family ID" and stored only until the end of the enrollment period. Once the site has filled all quotas, the Family ID will be permanently deleted.

For the purposes of scheduling, eligible participants will give their preferred name, nickname, or initials, which will allow RS to contact those who are unable to remain in clinic for a same day study visit.

Participants who cannot attend the study visit on the day of screening will also need to provide contact information. The contact information will be linked to their ATN SID. Contact information and preferred name/nickname/initials will be entered and stored in the "Scheduling Log" until the the end of the enrollment period

Data collected in all other questionnaires will be identified by a coded number only, to maintain participant confidentiality. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant (and parent or legal guardian, when applicable), except as necessary for monitoring by the ATN CC or NICHD.

11.2 Certificate of Confidentiality

To further protect the privacy of the study participants, the ATN has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). With this certificate in place, the ATN researchers cannot be forced to turn over identifying information about a study participant in any federal, state, or local criminal, administrative, legislative, or other proceedings. This certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study participant.

11.3 Risks and Benefits

11.3.1 Risks

Risks to participants in this research study may include:

Risk Category: Research not involving greater than minimal risk (45 CRF §46.404 and 21 CFR §50.51)

Participation in this study poses no more harms or discomforts to research participants than they may experience in normal daily life, standard clinical practice, during routine physical or psychological examinations or tests.

However, there are some risks of emotional discomfort or distress due to the personal nature of some questions asked in the CASI and debriefing interviews. Participants will be informed they are free to decline to answer any questions, or withdraw from participation at any time without penalty. Participants will be instructed to contact study personnel or to consult the list of referrals provided if feelings persist or worsen after several days. If the response indicates the participant is in urgent need of mental health assistance, RS should follow their individual site procedures for acute mental health referrals. RS should contact a supervisor immediately and stay with the study participant until the supervisor, mental health professional or emergency services, if needed, arrives.

11.3.2 Benefits

There are no individual benefits of participation; however, information from this study may benefit other youth, now or in the future, by understanding how to balance the risks of social harm due to participation against the risk of research-related harm.

11.4 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent documents and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for the oversight of the study. We will consent all participants verbally, as a signed consent form would be the only identifying information to link them to the study. We will use study information sheets in lieu of consent forms. The study information sheets describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

The study team is requesting the waiver of parental permission for minor participation based on 45 CFR 46.408, which provides that the IRB may waive parental permission under the same circumstances that it may waive individual consent, as described in 45 CFR 46.116 (d): (1) the research involves no more than minimal risk to participants; (2) the waiver or alteration will not adversely affect the rights and welfare of the participants; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the participants will be provided with additional pertinent information after participation. This research clearly meets requirements 1 & 2.

Assent of the children involved in this study will be sought in accordance with the regulations at 45 CFR §46.408(a) or 21 CFR §50.55 and local IRB/EC-approved policies and procedures.

11.5 Waiver of the Requirement for Parental Permission for Special Circumstances

The IRB of record will be requested to grant waiver of parental permission to participate in this research study for youth participants under the age of 18.

Under 45 CFR 46.408 (c), an IRB has the authority to waive parental permission if it determines that "a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects" and "an appropriate mechanism for protecting the children who will participate as research subjects is substituted" and "that the waiver is not inconsistent with Federal, State, or local law."

The protocol team would submit that this study is not considered greater than minimal risk. None of the content of this study is beyond what would be covered during routine medical or psychological visits. The probability of harm from participating in this study is no greater than that occurring in routine care.

The ATN sites involved in the study and most other community agencies offering HIV-related services are confidential and do not require parental/legal guardian notification or permission to treat under state regulations.

Contacting a parent/legal guardian could constitute a breach of confidentiality for these adolescents, as the study eligibility criteria indicate the adolescent is engaged in high-risk sexual activity of which his/her parent may not be aware. We do not wish to expose adolescent participants to the risk of social harm due to breach of confidentiality regarding their behavior and/or gender identity and/or sexual orientation.

11.6 Waiver of the Requirement for Signed Consent Form

We propose using a verbal consent process for study participation. The study information sheets describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

The study presents minimal risk to participants and involves no procedures that would require written consent outside of a research context. Under these conditions the IRB is authorized to modify the requirements for documented consent, or waive consent altogether (45 CFR 46.117 [c]).

11.6.1 For Study Participation

Street address, name, and contact information will be removed at the end of study enrollment, thus, a signed consent form would be the only permanent link between participants' identities and the study. In order to maintain the anonymity of the survey and fully protect the privacy of the volunteer study participants, the IRB will be requested to waive the requirement for a record of a signed consent form. A study information sheet (contains all elements of informed consent) will be reviewed with each potential study participant and provided to each participant who enrolls in the study. This form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

Under 45 CFR §46.117 (c) (1) and (2), an IRB may waive the requirement for the investigator to obtain a singed informed consent for some or all of the subjects if it finds either: (1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant will be asked whether he/she wants documentation linking him/her with the research, and the participant's wishes will govern; or (2) that the research presents no more

than minimal risk of harm to the participants and involve no procedures for which written consent is normally required outside the research context."

The protocol team believes that both #1 and #2 applies to this study and, both combined, justify waiver of written consent.

11.7 45 CFR Parts 160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" Pursuant to the Health Insurance Portability and Accountability Act - HIPAA)

The IRB will serve as the privacy board and will be asked to grant a waiver of HIPAA authorization for the study.

11.8 Study Discontinuation

This study may be discontinued at any time by the NICHD.

12.0 PUBLICATION OF RESEARCH FINDINGS

NICHD and ATN policies will govern publication of the results of this study. Publication of the results of this trial will be governed by ATN Publications Policy, which will be established the Publications Committee. Any presentation, abstract or manuscript will be made available for review by the Publications Committee prior to submission.

13.0 REFERENCES

1. CDC. HIV Among Youth. 2015; http://www.cdc.gov/hiv/group/age/youth/. Accessed January 15, 2017.
2. Haberer JE, Baeten JM, Campbell J, et al. Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa. *PLoS Med.* 2013;10(9):e1001511.
3. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med.* 2012;367(5):423-434.
4. MacQueen KM, Karim QA. Practice brief: adolescents and HIV clinical trials: ethics, culture, and context. *The Journal of the Association of Nurses in AIDS Care : JANAC.* 2007;18(2):78-82.
5. Chavez N, Williams, CY, Ipp, LS, Catallozzi M, Rosenthal SL, Breitkopf CR,. Altruistic reasoning in adoelscent-parent dyads considering participation in a hypothetical seual health clinical trial for adolescents. *Research Ethics.* 2015.
6. Department of Health E, and Welfare,. *The Belmont report: Ethical principles and guidelines for the protection of human subjects of research.* Washington, D.C.1979.
7. Department of Health and Human Services. Protection of Human Subjects. In. *45 CFR 46*2009.
8. National Commission for the Proteciton of Human Subjects of Biomedical and Behavioral Research. *Research Involving Children: Report and Recommendations.* Washington, DC: Department of Health, Education, and Welfare;1977.
9. Resnick MD, Bearman PS, Blum RW, et al. Protecting adolescents from harm. Findings from the National Longitudinal Study on Adolescent Health. *Jama.* 1997;278(10):823-832.
10. Garofalo R, Mustanski B, Donenberg G. Parents know and parents matter; is it time to develop family-based HIV prevention programs for young men who have sex with men? *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2008;43(2):201-204.
11. Ford C, English A, Sigman G. Confidential Health Care for Adolescents: position paper for the society for adolescent medicine. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2004;35(2):160-167.
12. Culp L, Caucci L. State adolescent consent laws and implications for HIV pre-exposure prophylaxis. *American journal of preventive medicine.* 2013;44(1 Suppl 2):S119-124.
13. Weithorn LA, Campbell SB. The competency of children and adolescents to make informed treatment decisions. *Child development.* 1982;53(6):1589-1598.
14. Rojas NL, Sherrit L, Harris S, Knight JR. The role of parental consent in adolescent substance use research. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2008;42(2):192-197.
15. Reed JL, Huppert JS. Predictors of adolescent participation in sexually transmitted infection research: brief report. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2008;43(2):195-197.

16. Ott MA. Vulnerability in HIV prevention research with adolescents, reconsidered. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2014;54(6):629-630.
17. National Institutes of Health. An Open Label Demonstration Project and Phase II Safety STudy of Pre-Exposure Prophylaxis Use Among 15 to 17 Year Old Young Men Who Have Sex with Men (YMSM). 2015; https://clinicaltrials.gov/ct2/show/NCT01769456.
18. National Institutes of Health. Phase 2a Study of Dapivirine Ring in Adolescent Females. 2015; https://clinicaltrials.gov/ct2/show/NCT02028338.
19. Gilbert AL, Knopf AS, Fortenberry JD, Hosek SG, Kapogiannis BG, Zimet GD. Adolescent Self-Consent for Biomedical Human Immunodeficiency Virus Prevention Research. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2015;57(1):113-119.
20. Schenk KD, Friedland BA, Chau M, et al. Enrollment of adolescents aged 16-17 years old in microbicide trials: an evidence-based approach. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2014;54(6):654-662.
21. Nelson LR SN, Ott MA,. The influence of age, health literacy, and affluence on adolescents' capacity to consent to research. . *Journal of Empirical Research on Human Research Ethics.* In Press.
22. Hein IM, Troost PW, Lindeboom R, et al. Accuracy of the MacArthur competence assessment tool for clinical research (MacCAT-CR) for measuring children's competence to consent to clinical research. *JAMA pediatrics.* 2014;168(12):1147-1153.
23. Ott MA, Alexander AB, Lally M, Steever JB, Zimet GD, Adolescent Medicine Trials Network for HIVAI. Preventive misconception and adolescents' knowledge about HIV vaccine trials. *Journal of medical ethics.* 2013;39(12):765-771.
24. Knopf AS, Gilbert AL, Zimet GD, et al. Moral conflict and competing duties in the initiation of a biomedical HIV prevention trial with minor adolescents. *AJOB Empirical Bioethics.* 2016:1-8.
25. Jeste DV, Palmer BW, Appelbaum PS, et al. A new brief instrument for assessing decisional capacity for clinical research. *Archives of general psychiatry.* 2007;64(8):966-974.
26. Torsheim T, Cavallo F, Levin KA, et al. Psychometric Validation of the Revised Family Affluence Scale: a Latent Variable Approach. *Child Indic Res.* 2016;9:771-784.
27. Hartley JE, Levin K, Currie C. A new version of the HBSC Family Affluence Scale - FAS III: Scottish Qualitative Findings from the International FAS Development Study. *Child Indic Res.* 2016;9:233-245.
28. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support. *Journal of Personality Assessment.* 1988;52(1):30-41.
29. Kerr M, Stattin H. What parents know, how they know it, and several forms of adolescent adjustment: Further support for a reinterpretation of monitoring. *Dev Psychol.* 2000;36(3):366-380.
30. Shelton RC, Winkel G, Davis SN, et al. Validation of the group-based medical mistrust scale among urban black men. *J Gen Intern Med.* 2010;25(6):549-555.
31. Widman L, Choukas-Bradley S, Helms SW, Golin CE, Prinstein MJ. Sexual communication between early adolescents and their dating partners, parents, and best friends. *J Sex Res.* 2014;51(7):731-741.

32. Knopf AS, Bakoyannis G, Zimet G. Urban American women's willingness to participate in HIV vaccine trials. Paper presented at: Poster presentation at the biannual meeting of the International AIDS Society; July 20, 2016; Durban, South Africa.
33. Lally M, Goldsworthy R, Sarr M, et al. Evaluation of an intervention among adolescents to reduce preventive misconception in HIV vaccine clinical trials. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2014;55(2):254-259.
34. Geraci M. Linear Quantile Mixed Models: The lqmm Package for Laplace Quantile Regression. *J Stat Softw.* 2014;57(13):1-29.
35. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011;30(4):377-399.
36. Sandelowski M. Whatever happened to qualitative description? *Research in nursing & health.* 2000;23(4):334-340.
37. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qualitative health research.* 2005;15(9):1277-1288.
38. Miles MB, Huberman AM, Saldaña J. *Qualitative data analysis : a methods sourcebook.* Third edition. ed.
39. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res.* 2011;20(1):40-49.

APPENDIX I

Schedule of Evaluations

Evaluation (Procedure)	Screening Day 0	Pre-Entry Day 1-3	Entry Day XX
Determine eligibility and collect contact information using the web-based screening tool	X		
Contact eligible adolescents/parents to schedule their visit		X	
Participant consents to participate in the study			X
The participant will complete the demographic, social, and attitudinal measures by audio computer-assisted self-interview (CASI).			X
Participant will undergo a simulated consent process for hypothetical Study 1, modeled after ATN 113, is an open-label study of oral TDF-FTC.			X
Participant will complete the WTP/WTS scale(s) via CASI			X
The RS will administer the UCSD Brief Assessment of Capacity to Consent (UBACC) for hypothetical Study 1.			X
Participant will undergo a simulated consent process for hypothetical Study 2, modeled after HPTN 077, a Phase IIa trial of oral + injectable cabotegravir.			X
Participant will complete the WTP/WTS scale(s) via CASI			X
The RS will administer the UCSD Brief Assessment of Capacity to Consent (UBACC) for hypothetical Study 2.			X
Willing participants will participate in a debriefing interview, which will begin immediately after their 2nd UBACC.			X