

HIV Prevention Trials Network

LETTER OF AMENDMENT #3 TO:

HPTN 071

**Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART):
A cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa**

Protocol Version 3.0 dated 16 November 2015

DAIDS Protocol ID: 11865

Date of Letter of Amendment: 06 June 2017

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the HPTN 071 (PopART) study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their review and approval. This LoA must be approved by all responsible IRBs/ECs before implementation.

The information in this LoA affects the Sample Informed Consent Forms.

Upon receiving final IRB/EC and any other applicable regulatory entity approval(s) for this LoA, your site may implement immediately any activities included in the LoA that do not require consent, or that only require revision to consent forms you have previously registered with the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). For any activities included in this LoA that require the participant to sign a consent form that is newly introduced with this LoA (that is, that your site has not previously registered with PRO), your site must first submit the LoA registration packet to PRO, including any new consents, and receive notification of successful registration prior to commencing those activities. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files. Note that a signed investigator signature page must be included in the registration packet sent to PRO.

If the HPTN 071 (PopART) protocol is amended in the future, this LoA will be incorporated into the next version.

HPTN 071
Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART):
A cluster-randomized trial of the impact of a combination prevention package on
population-level HIV incidence in Zambia and South Africa

DAIDS ID:
11865

Final Version 3.0
16 November 2015

Letter of Amendment 3
06 June 2017

INVESTIGATOR SIGNATURE PAGE

A Study of the HIV Prevention Trials Network (HPTN)

Sponsored by:

Division of AIDS, National Institute of Allergy and Infectious Diseases
U.S. National Institutes of Health

Funded by:

National Institute of Allergy and Infectious Diseases
National Institute of Mental Health
Office of the United States Global AIDS Coordinator
Bill and Melinda Gates Foundation
US National Institutes of Health

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Name of Investigator of Record

Signature of Investigator of Record

Date

Summary of Revisions and Rationale

The HPTN 071 protocol v3.0, 16 November 2015 has been updated to reflect the changes listed in this Summary of Revisions and Rationale. All changes made are indicated in the next section, Implementation of the Protocol Modifications.

- 1) The protocol has been modified to include an *Adolescent Cross-Sectional Survey* that will collect data from young people in the standard-of-care arm of the study (Arm C).
- 2) The protocol has been modified to add two additional secondary objectives measuring the impact of the study intervention on TB outcomes.

The reason for the first revision is to allow the team to collect data in Arm C that will complement similar data collected by Community HIV-care Providers (CHiPs) in the intervention arms of the study (Arms A & B). Having data from both the intervention communities and the standard-of-care arm will enable measurement of the effect of the intervention on HIV testing uptake and linkage to care and treatment among 15-to 19-year-olds. It will also provide data on key process measures and socio-demographic correlates of uptake of HIV testing and linkage to care and treatment among this same age group.

The reason for the second revision is to allow the team to more fully assess the impact of the combination prevention package on TB outcomes. The HPTN 071 (PopART) study represents a unique opportunity to understand how a broadly-implemented community intervention targeting both HIV and TB affects TB in the community. For the most part, the data needed to assess these outcomes are already collected, and only require additional analysis. An important set of data for addressing these objectives is the health center records for *Population Cohort* members. The majority of *Population Cohort* members consented to the study team reviewing their health center data to more fully understand the impact of the intervention when they enrolled in the study, but a waiver is requested to collect these data for TB as well as HIV objectives.

For the following sections, colored strikethrough (example) indicates text that has been deleted from the protocol. Colored underline (example) indicates text that has been added to the protocol. Ellipses within brackets ([...]) indicate areas where text from the protocol has not been shown, to reduce the length of this document. In the sample informed consent forms, bold text in brackets ([example]) indicates language that sites may alter, or not include, in their locally-adapted consent forms, depending on local requirements.

Revision 1- Addition of the Adolescent Cross-Sectional Survey

SCHEMA

Study Size: The combined population of all 21 clusters is approximately 1.2 million individuals. The interventions will be implemented in 14 of the 21 clusters with a combined population of approximately 800,000 individuals (adults and children) in the intervention arms. The approximate sizes of the randomly-selected groups for main study outcome assessments are:

- Population Cohort: 52,500 individuals
- Case-Control Studies: 1,600 individuals
- Qualitative Studies: about 2,000 individuals
- Adolescent Cross-Sectional Survey, Arm C: 1,400 individuals
- Population Cross-Sectional Survey: 10,500 individuals (if funded)

Note: Final sample sizes for surveys pending funding may change and will be described in separate protocol.

[...]

Secondary Objectives:

[...]

- Measure the effect of the intervention on HIV testing uptake and linkage to care and treatment among adolescents aged 15-19 years
- Collect data on key process measures and socio-demographic correlates of uptake of HIV testing and linkage to care and treatment among adolescents aged 15-19 years

[...]

OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME

• *Population Cohort*, Adolescent Cross-Sectional Survey, **Health Center Data**, **CHiPs Data**: uptake of PMTCT⁺, uptake of male circumcision⁺, ART screening and uptake⁺, uptake of HIV testing and retesting⁺, time between diagnosis and initiation of care⁺

2.2 Secondary Objectives

[...]

- Measure the effect of the intervention on HIV testing uptake and linkage to care and treatment among adolescents aged 15-19 years
- Collect data on key process measures and socio-demographic correlates of uptake of HIV testing and linkage to care and treatment among adolescents aged 15-19 years

[...]

2.3 Study Design

[...]

It is expected that the number of 15-19 year old CHiPs clients participating in the intervention will average approximately 2100 per community in each of the 14 intervention communities. For the Adolescent Cross-Sectional Survey, a target of 200 participants aged 15-19 years will be enrolled in each of the seven control communities. It is estimated that ~70-80% of the adolescents in the intervention communities will know their HIV status (following multiple rounds of testing in the community during the years of the trial) compared to an estimated ~35-45% in the control communities. Assuming a coefficient of between-community variation in the range $k=0.15$ to $k=0.20$ (among communities in the same matched triplet, and after accounting for the difference among the 3 study arms), we have >90% study power to show this difference in HIV status between control and intervention communities.

[...]

Section 5.6 Adolescent Cross-Sectional Survey, Arm C

The study team is interested in understanding the effect of the PopART intervention on adolescent members of the population for certain aspects of the study's secondary outcomes, such as uptake of HIV testing and uptake of ART. Community members younger than 18 are excluded from the PC, however, so there will be limited data available on adolescents in the PC

dataset. Data are collected from adolescent clients by CHiPs during the household intervention, and these data include information about HIV testing history, HIV care and treatment, and other topics of interest. However, because the household intervention is offered in Arm A & B communities only, these data are not available from Arm C, the standard of care arm. The goal of the Adolescent Cross-Sectional Survey is to collect data from adolescents in Arm C for comparison to the CHiPs-collected data from Arms A & B. To this end, the Adolescent Cross-Sectional Survey's primary objective is to determine the knowledge of HIV status (defined as self-reported HIV positive or having been tested and received an HIV negative result in the preceding 12) and linkage to HIV care and treatment in adolescents aged 15-19 years in the standard of care arm of the HPTN 071 (PopART) study. The survey also aims to collect data on variables that characterize HIV service uptake in the absence the PopART intervention package including socio-demographic correlates of uptake patterns.

5.6.1 Sampling/Recruitment of Adolescent Cross-Sectional Survey

There are seven Arm C communities. The recruitment goal of the cross-sectional survey is to enroll 200 adolescents aged 15-19 years per community, for a total of 1,400 participants.

5.6.2 Inclusion Criteria

- aged 15-19 years at the time of enrollment
- living in a block of houses randomly selected for recruitment
- responsible adult/parent/guardian has given permission for the Research Assistants (RAs) to interview the adolescent, for those aged <18 years.
- provide written informed consent

5.6.3 Exclusion Criteria

- being a participant in the *Population Cohort*
- anything that, in the opinion of the investigator, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

5.6.4 Procedures and Activities

Extensive community sensitization will take place to inform residents of the community about the aims and procedures for the survey prior to the beginning of recruitment. At each house, RAs will ask the responsible adult/parent/guardian for permission to enter the home and invite 15-19 year old household members to participate in the survey. The study will be explained to the adult/parent/guardian and adolescents. Written informed consent will be sought from all eligible adolescents present, and the RAs will make plans to return to the house to meet the other age-eligible adolescents at a time when they are expected to be at home.

The study procedure for participants will be completion of a survey. The questions for the first portion of the survey will be asked of the participant by the RA and will cover HIV status, HIV testing history, linkage to care, ART and TB symptoms and treatment. The RA will then plan to hand over the electronic data collection device so that the participant can self-administer the next part of the survey, covering socio-demographics, access to HIV-related services, sex education and sexual behavior, HIV-related stigma, STI symptoms, uptake of VMMC, pregnancy, drug and alcohol use, and mental health. Study participants will have the option, however, to have this component of the survey administered by the RA instead, if that is their preference. The RA will be available to guide those who choose to self-administer the

questionnaire. At the end of the survey, the RA will thank the participant and offer referrals for testing or other services.

Table 3- Study Activities across All Study Arms

Study Procedures/ Activity	Arm A	Arm B	Arm C
[...]			
Conduct of Case-Control studies			
Informed consent	X	X	
Completion of behavioral questionnaire	X	X	
<u>Conduct of Adolescent Cross-Sectional Survey</u>			
<u>Informed consent</u>			<u>X</u>
<u>Completion of survey</u>			<u>X</u>

¹Where these are already provided locally as standard services.

²ART eligibility according to local guidelines prior to protocol versions 3.0; immediate eligibility after full implementation of protocol version 3.0.

7.10 Outcomes for the Adolescent Cross-Sectional Survey

The primary outcome for data collected during the Adolescent Cross-Sectional Survey is the percentage of 15-19 year olds who know their HIV status. The primary analysis will be an analysis of variance of the 21 community-specific values of the percentage of 15-19 year olds who know their HIV status, including matched triplet and study arm as explanatory variables. This analysis will provide an estimate of the mean difference between Arm A and Arm C, and between Arm B and Arm C, for the percentage of 15-19 year olds who know their HIV status, together with a corresponding 95% confidence interval and p-value.

As a secondary analysis, we will use a 2-stage approach to adjust for individual-level characteristics that are determinants of knowledge of HIV status and so might confound our estimates of the differences among study arms.

7.11 Process Measures

[...]

- Uptake of male circumcision
 - Self-reported circumcision status/uptake at Enrollment, 12 months, 24 months, and 36 months of men in the *Population Cohort*
 - Uptake of circumcision in the community as indicated in health center data
 - Uptake of circumcision as indicated in data collected in households by CHiPs and in the Adolescent Cross-Sectional Survey

- ART screening and uptake
 - The proportion of *Population Cohort* members, identified as HIV-infected who screen for ART eligibility, and who subsequently initiate ART
 - Proportion of community members, identified as HIV-infected in data from CHiP teams, who screen for ART eligibility, and who subsequently initiate ART, as indicated in health center data
 - Proportion of HIV-infected adolescents who self-report being on ART from the data collected in households by CHiPs and in the *Adolescent Cross-Sectional Survey*
- HIV testing and retesting
 - Self-reported recent HIV testing at Enrollment, 12 months, 24 months, and 36 months in the *Population Cohort*
 - The number of adults (16 years and older) in the household and the number of HIV tests performed as indicated in data from CHiP teams and health centers
 - Self-reported history of HIV testing by adolescents from the data collected in households by CHiPs and in the *Adolescent Cross-Sectional Survey*
- Time between HIV diagnosis and initiation of care
 - The proportion of *Population Cohort* members initiating HIV care within 3 months of a positive HIV diagnosis
 - The proportion of community members initiating HIV care within 3 months of HIV diagnosis as indicated in data from CHiP teams (provision of HIV positive result) and health center data (date of care initiation)

Table 10- Summary of Study Objectives and Related Outcomes

PC= Population Cohort PX= Population Cross-Sectional Survey Ca-Co= Case-control CHiPs= Community HIV-care Providers

Objectives and Outcome Measures	Research Participants							Community members	
	PC at baseline	PC at 12m	PC at 24m	PC at 36m	PX at 36m ^a	Uptake Ca-Co	Qualitative Research	CHiPs Data (Arm A&B)	Routine Health Center Data
<i>Effect of the interventions on...</i>									
[...]									
Uptake of male circumcision									
<i>Self-reported circumcision status/uptake among cohort/survey participants</i>	X	X	X	X	X				
<i>Uptake of circumcision at health centers</i>									X
<i>Self-reported uptake of circumcision in the community</i>								X ^e	
ART Screening and uptake									
<i>The proportion of cohort/survey members identified as HIV-infected who screen for ART eligibility, and who subsequently initiate ART</i>	X	X	X	X	X			X	X
<i>The proportion of community members identified as HIV-infected who screen for ART eligibility, and who subsequently initiate ART</i>								X ^e	X
Uptake of HIV testing and retesting									
<i>Self-reported recent HIV testing among cohort/survey</i>	X	X	X	X	X				
<i>Number of adults in households and the number of HIV tests performed in each community</i>								X	X
<i>Self-reported HIV testing among adolescents</i>								X ^e	
[...]									

^a Not currently funded. Will be implemented if funding can be acquired

^b Consent must be obtained to access health center records for *Population Cohort* members

^c Explanatory research related to the outcomes/objectives indicated

^d Cost and effectiveness objectives will be addressed through analysis of deidentified data from health centers regarding costs and clinic use, in addition to specific questions asked of the *Population Cohort*

^e Includes data collected at the household by CHiPs in Arms A & B and as part of the *Adolescent Cross-Sectional Survey* in Arm C.

Section 8.6.3 Individual Consent

[...]

Individual consent for research studies in all Arms

Written informed consent to participate in research will be required before enrolling individuals in the *Population Cohort, Case-Control studies* and *Adolescent Cross-Sectional Survey*.

Written informed consent will also be required of individuals participating in qualitative research activities that involve collection of participant-identified responses to interviewer questions (such as interviews and focus groups). However written consent will not be sought for other types of qualitative methods, such as observation of persons who are not participants.

Section 8.6.5 Waiver of Parental Consent in the Adolescent Cross-Sectional Survey

A waiver of parental consent will be sought for minors participating in the *Adolescent Cross-Sectional Survey*. Per the United States Code of Federal Regulations (45 CFR 46.408(c)), such a waiver is permissible if the ethics committee determines that for the situation, parental or guardian permission is not a reasonable requirement, and an appropriate mechanism for protecting the children participating in the research will be provided.

For the following reasons, the study team believe that obtaining parental or guardian consent is not a reasonable requirement for the *Adolescent Cross-Sectional Survey*:

- It is assumed that if parental consent were required, there would be a significant risk that some participants might feel compelled to participate to acquiesce to their parents' will.
- Some questionnaire items are private, and most participants would not want their parents knowing the detail of their answers. If, through the act of obtaining parental consent, the participants came to suspect that their parents might learn their answers, then this risks the participants misrepresenting their answers due to social desirability bias. Such bias would invalidate the evaluation. Therefore, getting truthful data, broadly representative of the young people in the community, may be practicably difficult without the waiver of parents' consent.
- Apart from the 15 year olds in Zambia, the age range of the participants being recruited for this survey is commensurate with the ages at which local guidelines allow persons to consent for themselves for an HIV test, indicating that local authorities recognize this as an age at which individuals can comprehend what is being asked of them and can make an informed choice.
- Establishing biological parenthood or legal guardianship – and not *de facto* caregiving of a grandparent, aunt, or informal foster parent – is very difficult and can be embarrassing for families. Attempting to verify parenthood or legal guardianship both (a) potentially introduces disruption into the family unit, and (b) risks falsification by people who are not biological parents or legal guardians but want the children in their home to participate. If this is unnecessary without compromising the participants' autonomy, then it should be avoided.
- Participants in the survey are 15-19 years old. This means that if parental consent is required, then there will be separate consent procedures for 15-17 year olds and for 18-
- 19 year olds. This could cause confusion, particularly in homes with multiple participants. Further, it risks reinforcing the 15-17 year olds' lack of autonomy compared to their not-much-older peers.

- The research is low risk, only involving completion of a questionnaire. No participant will be exposed to an experimental or medical procedure.

The Community Advisory Boards (CABs) for both the adolescent survey and parent trial recommended a waiver of parental consent in both countries and full written consent by all adolescent participants, including the 15-17 year olds.

The following are the steps planned as an alternative mechanism to parental consent to safeguard the welfare of the adolescents asked to participate in the survey:

- The study team will conduct a full written informed consent with each participant so that they understand the procedures, risks, benefits of participation before agreeing to participation. As noted above, the adolescents to be recruited for this study are of an age commensurate with the age at which local authorities have determined individuals can comprehend what is being asked of them and can make an informed choice.
- The study team will inform communities about the survey to facilitate community support and to ensure that parents understand why their children and not they are being asked to consent. This activity will minimize the likelihood that an adolescent's participation in the survey will be viewed with suspicion by parents or result in social harm.
 - Members of the main HPTN 071 (PopART) CAB and the adolescent survey CAB will inform community members about the study – including the waiver of parental consent – on relevant community platforms in the months in advance of the survey
 - A team of community mobilisers will visit the data collection zone a week or two in advance of the RA team. This mobilization team will sensitize residents – parents and potential participants – about the study and the processes
 - On the day of data collection, RAs will ask verbal permission from the responsible adult to (a) enter the home, and (b) approach 15-19 year old residents. Parents who do not want their children to participate can still opt out on behalf of their children.
 - All research participants will sign a full written informed consent
- To further safeguard the rights and well-being of the adolescents in the study, two CAB members will be identified for each study community to act as advocates for the minors in the survey. Their roles will include but will not be limited to:
 - Providing a point of contact and first referral should the participant or their familial custodian have a concern about the survey that they are not comfortable addressing to study staff or the ethics committee
 - Maintaining an up-to-date understanding of the study protocol and the study population, to allow the advocate to answer participants' (or their familial custodians') questions about the study, and to advocate with the study team about any issues that arise, representing participants' best interests
 - Facilitating the participant's linking to an appropriate advocacy, ethics, or legal body should any matter require escalation

Appendix VII – - Sample Informed Consent Form –Adolescent Cross-sectional survey

PARTICIPANT INFORMATION AND CONSENT FORM

Title of Research Study: Uptake and acceptability of a combination HIV prevention package among young people in Zambia and South Africa – PopART for Young people (P-ART-Y)

A sub-study of

HPTN 071: Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART): A cluster-randomized trial of the impact of a combination prevention package on population-level HIV incidence in Zambia and South Africa (DAIDS ID: 11865)

Sponsor: Division of AIDS (DAIDS)
United States (US) National Institute of Allergy and Infectious Diseases (NIAID)
US National Institutes of Health (NIH)

Investigator of Record: *(insert name)*

Research Site Address: *(insert address)*

Daytime telephone number(s): *(insert number)*

24-hour contact number(s): *(insert number)*

Subject Information and Consent Form

Please ask the study investigator or the study staff to explain any words or procedures that you do not clearly understand.

The purpose of this form is to give you information about the research study you are being asked to join. If you sign this form, you will be giving your permission to take part in the study. The form describes the purpose, procedures, benefits, and risks of the research study.

Please read this Participant Information and Consent Form and ask as many questions as needed. You should not sign this form if you have any questions that have not been answered to your satisfaction.

This study is being funded by the UK Department for International Development, Southern Africa.

Your participation is voluntary

You do not have to take part in this study. Even if you decide to take part now, you may refuse any portion of the study or stop at any time. Choosing not to participate or to withdraw will not affect the care you receive at the health centers in your community.

Purpose of the research

The HPTN 071 or PopART study is testing whether a combined HIV prevention package can reduce new HIV infection in communities like yours. The PopART for Youth (P-ART-Y) study is a sub-study to understand how well the PopART prevention package works for young people aged 15-19 years old. In P-ART-Y, we want to see if more young people know their HIV status in places where there is the PopART intervention package compared to places without this intervention.

Why am I being asked to participate?

We are asking you to participate because you are aged between 15 and 19 years and live in a randomly-selected block of houses in one of the seven study communities receiving the standard of care package in the HPTN 071 study. In total, we plan to conduct this survey with approximately 200 young people aged 15-19 years in each of these seven communities – 1400 overall.

What will happen during this study?

If you participate in this study, you will be asked to complete a one-time survey that will take approximately 30-45 minutes. The survey asks a range of questions about your experiences of HIV testing. The questionnaire also asks about your experiences accessing health services, learning about HIV and sex, your sexual practices and experiences, and general health issues like alcohol use and mental well-being.

You DO NOT have to test for HIV as part of the study. However, if you want to know your HIV status, we will refer you to your nearest local clinic. The study team will be available to help you access HIV counselling and testing services and other counselling services from your local clinic if you feel like you need them after completing the questionnaire.

What are the possible risks or discomforts?

You may become embarrassed, worried or anxious when answering some survey questions. To minimize any discomforts, we have made some of the questions self-administered meaning that you will not have to answer aloud, if you choose not to. Instead you will select your answers directly on the data collection device. A trained staff member will help you deal with any feelings or questions you have. You do not have to answer any question that you do not want to answer.

What are the potential benefits?

The direct benefit from study participation will be minor, but you may feel good about having represented your communities and providing feedback about the uptake of HIV testing and other related issues among young people in communities like yours. In addition, knowledge gained from this study will help us understand how better to deliver HIV services to young people in Southern Africa.

How will my confidentiality and privacy be protected?

You will complete the survey anonymously. This means that we will not record your name with your survey responses. The only place that we record your name is on this participant informed consent form. All electronic data are kept on password protected databases and any paper documents containing data are kept in locked cabinets. To protect your privacy, please help the researcher to identify a space where you feel comfortable answering the questions and others cannot overhear you. When you enter your answers into the device, you will have control over who else can see what is on the device's screen.

People who may review the study data include: [insert name of site IRB/EC], local regulatory agencies, US National Institutes of Health (NIH), study staff, and study monitors. Institutional Review Boards (IRBs) or Ethics Committees (ECs) are committees that watch over the safety and rights of research participants.

What happens if I am injured by participating in this study?

It is very unlikely that you could be injured as a result of participating in this study. However, if you are injured while participating in this study, then we will pause/stop administering the questionnaire with you so that you can seek medical assistance. There is no program for compensation through the United States NIH. You will not be giving up any of your legal rights by signing this participant information and consent form.

Persons to Contact for Problems or Questions

If you have any questions about your participation in this research study or your rights as a research participant, you may contact:

Investigator of Record Name: (site insert name of the investigator or other study staff)

Research Site Address(es): (site insert physical address of above)

Daytime telephone number(s): (site insert telephone number)

24-hour contact number(s): (site insert telephone number)

If you have any questions or concerns about your rights as a research subject or want to discuss a problem, get information or offer input, you may contact:

Independent Review Board/Ethics Committee: (site insert name or title of person on the IRB, EC or other organization appropriate for the site)

Address of Independent Review Board: (site insert physical address of above)

Daytime Telephone Number: (site insert telephone number of above)

Below are the names of two additional people you may contact if you have any questions or concerns about the study. They are members of this community who participate locally on the study's community advisory board and have volunteered to act as advocates for the young people participating in the study.

Youth Advocate 1: (site insert name or title of person)

Daytime Telephone Number: (site insert telephone number of above)

Youth Advocate 2: (site insert name or title of person)

Daytime Telephone Number: (site insert telephone number of above)

PARTICIPANT'S STATEMENT OF CONSENT

Uptake and acceptability of a combination HIV prevention package among young people in Zambia and South Africa – PopART for Young people (P-ART-Y)

- I have been given sufficient time to consider whether to take part in this study.
- My taking part in this research study is voluntary. I may decide not to take part or to withdraw from the research study at any time without penalty or loss of benefits or treatment to which I am entitled.
- I have had an opportunity to ask my study investigator questions about this research study. My questions so far have been answered to my satisfaction.
- I have been told how long my participation in the research study will take.
- I have been told that my participation will mean answering a questionnaire.

- I have been told what the possible risks and benefits are from taking part in this research study.
I may not benefit if I take part in this research study.
- I do not give up my legal rights by signing this form.
- I have been told that before any study related procedures being performed, I will be asked to voluntarily sign this Participant Information and Consent Form.
- I will receive a signed and dated copy of this Participant Information and Consent Form.

If you have either read or have heard the information in this Participant Information and Consent Form, if all of your questions have been answered, and if you agree to take part in the study, please print and sign your name and write the date on the line below.

I voluntarily agree to take part in this research study.

Participant's Name (print) Participant's Signature and Date

I certify that the information provided was given in a language that was understandable to the subject.

Name of Study Staff Study Staff Signature and Date
Conducting Consent Discussion (print)

Witness' Name (print) Witness' Signature and Date
(As appropriate) Date

SCHEMA

Secondary Objectives:

- Measure the impact of the two intervention packages on the following:
 - [...]
 - Case notification rate of tuberculosis and the clinical characteristics and treatment outcomes of tuberculosis cases
 - [...]
 - Uptake of tuberculosis screening offered at the household level and the characteristics of tuberculosis cases identified through and missed by such screening

OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME

- ***Population Cohort and Health Center Data:*** ART Adherence⁺, HIV disease progression and death⁺, ART toxicity⁺, HIV stigma ^{*}, TB notifications, clinical characteristics and treatment outcomes including mortality rate among TB cases
- ***Population Cohort, Health Center Data, CHiPs Data:*** uptake of PMTCT⁺, uptake of male circumcision⁺, ART screening and uptake⁺, uptake of HIV testing and retesting⁺, time between diagnosis and initiation of care⁺, cascade of TB screening and characteristics of TB cases identified through and missed by screening

1.2.4 Innovation

[...]

Fourth, the universal test and treat strategy being investigated in the HPTN 071 study is likely to have a significant effect on TB [91, 92]. On an individual level it is well established that TB is increasingly common at lower CD4 cell counts. However, the risk of developing TB increases rapidly after acquisition of HIV [93]. ART has been shown to reduce the risk of developing TB in individuals by increasing CD4 cell counts [94]. The effects of ART on TB at community level are not known. The study will assess impact of the intervention on TB as determined from health center records, Population Cohort data and CHiPs data, and so begin to address this important question.

[...]

2.2 Secondary Objectives

- Measure the impact of the two intervention packages on the following:
 - [...]
 - Case notification rate of tuberculosis and the clinical characteristics and treatment outcomes of tuberculosis cases
 - [...]
 - Uptake of tuberculosis screening offered at the household level and the characteristics of tuberculosis cases identified through and missed by such screening

3.12.1 Activities with Local Health Centers/Community Institutions

[...]

The home-based HIV testing and TB screening that is carried out by the CHiP teams will be captured on the CHiPs electronic data collection device. (These data are stored on the device in encrypted form and are accessible only to authorized users after entry of an individual username and password.) To the degree possible, the study team will obtain data from

electronic patient record systems at the healthcare facilities on those clients documented as having consented to the CHiPs intervention who are captured in the CHiPs electronic database. This linkage will provide feedback to CHiPs on whether clients need further support to obtain care and will help the team to estimate the proportion of HIV-infected individuals who register for HIV care following an HIV diagnosis, and the time from HIV diagnosis to HIV care registration. Similarly, TB screening process indicators, including the characteristics of TB cases identified and missed by the TB screening intervention, will also be explored using overall CHiPs data and through linkage of CHiPs data to TB data at the healthcare facilities. In Arms A and B, but not Arm C, there will be active follow-up of HIV-infected individuals who have been referred for HIV care by CHiP teams, but who have not registered for HIV care. CHiP teams will also provide additional support for retention in HIV care and ART adherence, contributing to active follow-up of individuals who have missed scheduled visits. If an individual has left the community, they will not be followed up outside the community.

5.0 RESEARCH PROCEDURES AND ACTIVITIES

The deployment of the interventions among the communities assigned to Arms A and B is expected to lower HIV incidence throughout the communities. Measurement of HIV incidence, however, will occur in a subset of adults enrolled into the *Population Cohort* in each study community and followed longitudinally. Secondary outcomes (among them process measures, TB outcomes and qualitative research aims) will also be measured from data provided by this cohort, from routinely-collected health center data, and from data collected by CHiPs during household visits. Other secondary outcomes will be measured from qualitative and case-control studies, and, if funded, from additional one-time surveys. Research activities, including identification and consent of participants, conduct of study procedures, and retention-related activities, will be performed by a trained research team, separate from the CHiP teams that will be responsible for delivering the intervention to the community-at-large. A table summarizing the secondary objectives and outcomes, including the source of outcome data, is provided in Section 7.11.

[...]

5.1.5 Reviewing Health Center Records for Population Cohort

For HIV-infected *Population Cohort* members who provide consent to access their health clinic records, the study team will attempt to link the research data to routine electronic HIV care data that are collected at the health center, to measure HIV disease progression and death, ART toxicity, and the time between HIV diagnosis and initiation of HIV.

For all *Population Cohort* members who provide consent to access their health clinic records, the study team will also attempt to link the research data to routine TB data held at the health center, to measure notified TB incidence and the clinical characteristics and treatment outcomes of notified TB cases in the cohort. Where possible, TB outcomes will be stratified by HIV status (including CD4 cell count, ART status etc).

5.5.1 Tuberculosis Case Notification

TB cases in the study communities are routinely diagnosed and treated at the same health centers as those delivering HIV treatment and care. In all of the study communities, the TB notification process will be strengthened by the use of additional diagnostic tests and enhanced monitoring of the TB case registration system. Data from this system will be compiled at regular intervals during the trial and used to measure the following outcomes:

- Notification rate of bacteriologically confirmed pulmonary tuberculosis
- Notification rate of all tuberculosis
- The clinical characteristics and treatment outcomes including mMortality rate of bacteriologically confirmed pulmonary tuberculosis

- The clinical characteristics and treatment outcomes including mortality rate of all tuberculosis

These data will be collected for each time period, and will be classified according to HIV status (including CD4 cell count, ART status, etc.) where possible. Outcomes will be compared across study arms.

As far as possible, health center TB data will also be linked to Population Cohort data, which will enable the outcomes described above to be determined for the cohort (section 5.1.5). Triangulating outcomes in the cohort with outcomes in the overall community will allow more robust conclusions regarding the intervention effect on TB. Health center TB data will also, where possible, be linked to CHiPs data and to other data sources used to facilitate the referral of community members for TB diagnosis and treatment (e.g. TB suspect registers). This will enable the process measures and characteristics of TB cases identified and not identified through TB screening to be explored in more detail.

5.5.6 Uptake of Intervention Components

Process measures of the uptake of key components of the intervention will be measured in Arms A and B using data from the health centers on the rates of utilization of PMTCT services and medical male ~~and~~ circumcision, the proportion of community members initiating HIV care within three months of receiving an HIV diagnosis and the proportion of community members initiating TB treatment following a TB diagnosis.

7.6 Outcomes for Secondary Objectives

[...]

- Case notification rate of tuberculosis
 - Case notification rates of bacteriologically-confirmed TB and all TB diagnosed among the general population of patients seeking care at health centers as recorded by health centers
 - Case notification rates of bacteriologically-confirmed TB and all TB diagnosed in members of the Population Cohort
 - The clinical characteristics and treatment outcomes including TB mortality among TB cases in the community as recorded by health centers
 - The clinical characteristics and treatment outcomes including TB mortality among TB cases in members of the Population Cohort

[...]

7.11 Process Measures

Several process measures will be recorded in Arms A, B, and C to evaluate the implementation and delivery of the PopART interventions. These measures evaluate processes that are intermediary between the provision of the intervention and achievement of the primary outcome. These measures will be important therefore in understanding how and why the intervention is (or is not) successful in producing that outcome. Further, those data that are collected from CHiP teams or health centers (as opposed to research cohorts) can be reviewed by the study team during the study period and can be used to make real-time adjustments to deployment of the intervention to improve its effectiveness. In addition to the process measures relating to the primary outcome detailed below, TB screening process measures will also be

evaluated. CHiPs data will be used to summarise the cascade of TB screening (e.g. the proportion positive on TB screening, the proportion diagnosed with TB, the proportion starting TB treatment etc) both overall, and where possible, by age, gender, HIV status and other socio-demographic characteristics. In addition, the characteristics of TB cases identified and missed by the TB screening intervention, will also be explored through linkage of CHiPs data to TB data at the health centers (also see section 3.12.1 and 5.5.1.)

Table 10- Summary of Study Objectives and Related Outcomes

PC= Population Cohort PX= Population Cross-Sectional Survey Ca-Co= Case-control CHiPs= Community HIV-care Providers

Objectives and Outcome Measures	Research Participants							Community members	
	PC at baseline	PC at 12m	PC at 24m	PC at 36m	PX at 36m ^a	Uptake Ca-Co	Qualitative Research	CHiPs Data (Arm A&B)	Routine Health Center Data
<i>Effect of the interventions on...</i>									
[...]									
Case notification rate of tuberculosis									
<i>Case notification rates of bacteriologically-confirmed TB and all TB^b</i>	X	X	X	X					X
<i>Clinical characteristics and treatment outcomes including TB mortality among TB cases^b</i>	X	X	X	X					X
[...]									
Uptake of HIV testing and retesting									
Uptake of TB screening and clinical characteristics of TB cases identified and missed by TB screening									
<i>The proportion positive on TB screening</i>								X	
<i>The proportion diagnosed with TB due to TB screening</i>								X	X
<i>The proportion starting TB treatment due to TB screening</i>								X	X
<i>The characteristics of TB cases identified and missed by TB screening</i>								X	X
[...]									

8.5.2.2 Risks

[...]

Community members who report to the health center to undertake HIV care (including ART) ~~or to receive HIV testing~~ or to receive TB diagnosis/treatment will have sensitive data collected in clinic records, some of which will be then be harvested into an electronic research database. Most of these research data will be collected without personal identifiers (except TB data which will be collected with personal identifiers for data linkage purposes), but research cohort members may provide consent for use of identified data. Collection and storage of sensitive health information carries with it the risk of unwanted disclosure if there is a breach of data security or incomplete removal of personal identifiers from “anonymous” data sets.

[...]

8.6.6 Waiver of Consent- Clinic Data for TB Objectives

A waiver of consent will be sought to allow study staff to collect TB-related data at the health center for participants who have consented to allow their health center records to be accessed and used for this study, without requiring a separate consent for this particular use. The reasons for requesting this wavier are:

- Written voluntary informed consent is sought from all *Population Cohort* members to access health center data at the time of enrollment. This consent is sought irrespective of HIV status and the language of the consent is broad (“My initials indicate that I agree to allow my records at the health center to be accessed and used for this study”). The language in the body of the consent, however, frames the request to access health center records in terms of understanding the effect of study activities on the health of people who are diagnosed with HIV, and so a waiver is sought to access participants’ data, irrespective of the participant’s HIV status, to address TB-specific endpoints without going back to re-consent all participants for this particular use.
- The HPTN 071 (PopART) study presents a unique opportunity to assess the effect of a broadly-implemented community intervention targeting both HIV and TB on TB outcomes. Accessing these data is important to address these research objectives.
- The burden of this additional access on the privacy of the participants is minimal.
- Conducting this research would be impracticable if a waiver were not allowed. There are over 40,000 *Population Cohort* participants distributed across the country of Zambia and the Western Cape of South Africa. Greater than 90% of these participants provided consent to allow the team to access their health center records. To obtain specific written consent from these participants to look at their TB-related data in the health care center records would be burdensome enough that the research could not be done.