

## **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**

## **Statistical Analysis Plan**

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## A Introduction

This statistical analysis plan (SAP) details the statistical procedures that address the study objectives specified in Protocol version 1.0 of the HPTN071 (PopART) Study: 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

New versions of the SAP will be issued to document updates and changes in the plan. Any meaningful changes or additions to this SAP (e.g., in response to protocol amendments or violations of assumptions underlying pre-planned analyses), and the timing of such changes will be documented in Section B.1 and B.2 and further described in an Appendix of the SAP, as necessary. Analysis plans for sub-studies not addressed in the protocol, and for secondary analyses not anticipated prior to study completion, will be developed as separate documents. Specifically, the following study components are not included in the SAP

1. Mathematical modeling
2. Case-control studies
3. Economic modeling
4. Ancillary studies

Formal interim monitoring will not be implemented in the study since intervention effects are expected to become stronger with each year of the intervention and reliable assessments of emerging data on the primary endpoint will likely not be available until some months after the completion of each PC round. Plans for interim monitoring of intermediate outcomes are outlined in Section H.

In addition to DSMB reviews, the PopART data team will routinely report on operational metrics (e.g., rates of recruitment and retention, intervention uptake) to the study operations team, which will communicate with sites concerning operational performance based on these metrics. No analysis of HIV incidence or community viral load will be included in these reports, the format and schedule of which are not considered further in this SAP.

## B Study Objectives and Summary

This section corresponds to the protocol (Version 1.0). Changes to the protocol that affect the statistical analysis plan will be noted in Section B.1

**Purpose:** The purpose of this study is to determine the impact of two community-level combination prevention packages, both of which include universal HIV testing and intensified provision of HIV antiretroviral therapy (ART) and care, on population-level HIV incidence.

**Design:** This is a three-arm, cluster-randomized, longitudinal study to be implemented in 21 clusters (communities).

**Study Population:** The prevention packages will be implemented throughout the communities randomized to the intervention arms. Main study outcomes will be measured in a randomly-selected group drawn from the adult population of the communities: *A Population Cohort*.

**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:* 2,400 individuals
- *Qualitative Studies:* about 2,000 individuals
- *Population Cross-Sectional Survey:* 10,500 individuals (if funded)
- *TB Survey:* about 56,000 (Arms A and B) individuals (if funded)
- *CHIPS:* about 150,000 households; 300,000 adults.

#### **Study Arms/Interventions:**

##### **Arm A - Universal Testing with Immediate ART:**

- Combination prevention package including:
  - House-to-house deployment of:
    - Universal HIV counseling and testing
    - Active linkage to care for individuals diagnosed as HIV-infected, with ***immediate eligibility for ART***
    - Promotion of male circumcision and prevention of mother-to-child transmission (PMTCT) services
    - Provision of condoms
  - Strengthening of HIV testing and services at health facilities and other venues
  - Strengthening of male circumcision and prevention of mother-to-child transmission of HIV services available in the community
  - Treatment of sexually transmitted infections (STIs) and provision of condoms at health units

##### **Arm B - Universal Testing with ART Eligibility According to National Guidelines:**

- Combination prevention package including:
  - House-to-house deployment of:
    - Universal HIV counseling and testing
    - Active linkage to care for individuals diagnosed as HIV-infected, with ***ART eligibility according to national guidelines***
    - Promotion of male circumcision and PMTCT services
    - Provision of condoms
  - Strengthening of HIV testing and services at health facilities and other venues
  - Strengthening of male circumcision and PMTCT services available in the community
  - Treatment of STIs and provision of condoms at health units

##### **Arm C - Standard of Care (Control Arm)**

- Strengthening of HIV testing and ART services according to national guidelines at health facilities and other venues
- Strengthening of male circumcision and PMTCT services available at health facilities and other venues in the community
- Treatment of STIs and provision of condoms at health facilities and other venues in the community

**Study Duration:** The planned duration of the entire study will be approximately 6 years, with enrollment and follow-up of communities and delivery of the intervention occurring over 4 years. Assessment of the primary outcome (HIV incidence) in the *Population Cohort* is planned to take place 12, 24, and 36 months after recruitment. Interim evaluation will take place during the first two years of intervention to determine whether to continue with the 36-month follow-up of the *Population Cohort* and the fourth year of intervention.

**Primary Objective:**

- To measure the impact of the two intervention packages on HIV incidence by enrolling and following a random sample of adults (the *Population Cohort*) in the trial communities for 3 years

**Secondary Objectives:**

- Measure the impact of the two intervention packages on the following:
  - HIV incidence over the first, second, and third years of follow-up
  - Community viral load (if funding is identified)
  - ART adherence and viral suppression (if funding is identified)
  - ART drug resistance (if funding is identified)
  - HSV-2 incidence
  - Uptake of HIV testing and retesting over the entire study period
  - ART screening and uptake
  - Time between HIV diagnosis and initiation of care
  - Retention in care
  - HIV disease progression and death
  - ART toxicity based on clinic records
  - Sexual risk behavior
  - Case notification rate of tuberculosis
  - HIV-related stigma
  - Uptake of PMTCT
  - Uptake of male circumcision
- Carry out case-control studies to examine factors related to:
  - Uptake of HIV testing during the first round of home-based testing in Arms A and B
  - Uptake of immediate treatment in Arm A
  - Uptake of HIV testing during the second round of home-based testing in Arms A and B
- Use qualitative methods to:
  - Assess popular understanding of HIV testing and treatment at study initiation and during implementation
  - Evaluate the acceptability and functioning of the Community HIV-care Providers (CHiPs) in Arms A & B
  - Evaluate the acceptability of interventions and barriers to access in Arms A & B
  - Document the effect of the interventions on social networks, stigma, sexual behavior, alcohol use, gender-based violence, HIV identity, other HIV prevention options and community morale
  - Evaluate the process and challenges of community consultation and applying ethical principles

- Measure the burden experienced by local health centers due to implementation of the intervention in the community
- Measure the incremental cost of the two intervention packages through systematic recording of costs in intervention and control communities
- Estimate the effectiveness and cost-effectiveness of the intervention packages and alternative packages, both in the chosen study populations and in other populations by fitting mathematical models based on the empirical data from the trial, including data related to cost.

**Study Sites:** The study is implemented in the communities identified below.

- The study communities in Zambia are spread across 4 provinces and 5 districts. Each community is the catchment population of a government health facility.
  - Chimwemwe and Ndeke in Kitwe District (Copperbelt Province)
  - Chipulukusu and Chifubu in Ndola District (Copperbelt Province)
  - Makululu and Ngungu in Kabwe District (Central Province)
  - Chawama, Chipata and Kanyama in Lusaka District (Lusaka Province)
  - Maramba and Dambwa in Livingstone District (Southern Province)
  - Shampande in Choma District (Southern Province)
- The study communities in South Africa are located in the Cape Metro District and Cape Winelands District of the Western Cape Province. As above, the communities are defined by the catchment population of a government health facility.
  - Delft South (Metro District)
  - Kuyasa (Metro District)
  - Luvuyo (Metro District)
  - Town II (Metro District)
  - Ikhwezi (Metro District)
  - Bloekombos (Metro District)
  - Dalevale (Cape Winelands District)
  - Wellington (Cape Winelands District)
  - Cloetesville and Idasvalei (Cape Winelands District)

## **B.1 Modifications of the Protocol Affecting the Statistical Analysis Plan**

### ***B.1.1 Version 2.0:***

Immediate offer of ART for all HIV infected individuals attending health care facilities will be implemented within all clinics involved in the HPTN071 (PopART) trial. This will be offered ahead of local guidelines once protocol version 3.0 is approved and funding to support the change can be secured.

Change to analysis plan:

The primary analysis for the assessment of the PopART impact on HIV incidence is unchanged, as the implementation of immediate offer of ART for all HIV infected individuals attending health care facilities did not affect Year 1 of the intervention and is likely to only partially impact outcomes in Year 2. Even in Year 3, as for the PopART intervention itself, effects will still take time to accumulate, especially for impact on HIV incidence.

A secondary analysis objective has been added to assess the impact of immediate treatment policies on community HIV incidence.

Addition of PC12N participants, enrolled during the second year of the cohort, in communities where fewer than 2000 participants were enrolled in PC0.

Change to analysis plan:

PC12N are included in the PC and will contribute endpoints as accumulated. In particular, HIV-uninfected PC12N participants will add to seroincidence and person years accumulated at PC24 and PC36.

Adjustments for age at baseline was changed to age at each visit in the primary analysis. The first stage in the primary analysis estimates expected incidence by age and sex. The modification was required because age at enrollment is not equivalent in PC0 and PC12N/PC24N participants.

### **B.1.2 Version 3.0**

Addition of PC24N participants, enrolled during the third year of the cohort in Arm A and C community, where sufficient remaining households exist.

PC24N are included in the PC and will contribute additional endpoints and person time for the PC24-PC36 period.

The proposed secondary analysis objective to assess the impact of immediate treatment policies on community HIV incidence was changed to exploratory and removed from the SAP.

## **B.2 Additional modifications to the Statistical Analysis Plan**

At the October 2016 DSMB review, the protocol team reviewed the mathematical modeling projections of potential intervention effect from the individual based model, which was based on the current data about intervention uptake. The DSMB approved a change to the primary endpoint of the trial from assessing the impact of the intervention over the three years of PC follow-up to considering only the second and third year of the PC. i.e., differences in seroincidence rate as measured at PC24 and PC36 only.

The approach to estimation of the standard error for the two-step analysis approach was modified to utilize the three arm design. In the previous version, different estimates of the test statistic standard error were used for Arm A vs Arm C and Arm B vs Arm C, each based on the communities in those arms, resulting in a 6 df t-test. However, it is more efficient to use the MSE from a two-way ANOVA to estimate the common standard error, resulting in the same SE for both comparisons and a t test with 12 df.

Prior versions of the SAP noted the possible use of a community level covariate adjustment for the two-stage analysis, which reduces the degrees of freedom for the primary comparison by 1. The protocol chair decided for the primary HIV incidence outcome to adjust the analysis for Baseline HIV Prevalence based on the following considerations:

- Overall balance in baseline HIV prevalence across arms is good, but there are some triplets where it is less good (notably Triplet 7)
- This might result in a large value for  $s$  (based on the between triplet variation in differences between study arms) which then reduces power
- If baseline prevalence is a good predictor of incidence, then adjustment for baseline should help to reduce  $s$

- The critical points for t with 11 and 12 df are very similar (2.18 and 2.20)

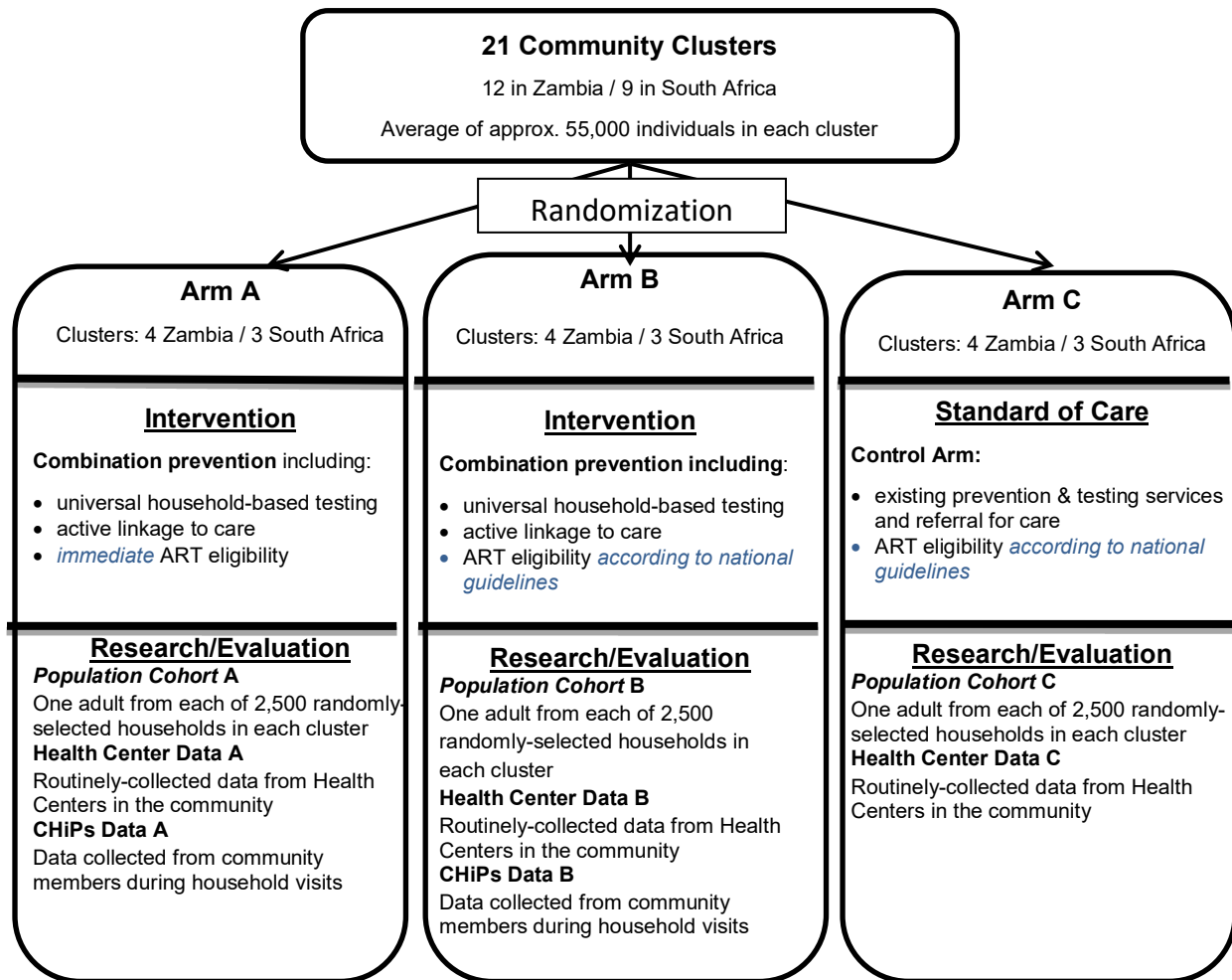
#### Version 3.0

- Clarification of the HIV testing included in defining “HIV status by study testing”
- Clarification of HIV seroconverter to include participants who are determined to be HIV-infected with acute infection
- Age adjustment for HIV incidence analysis will use the Lexis expansion method, to appropriately attribute partial person years to the correct age category in each year of participation.
- An additional subgroup was added for PC24 viral load suppression: Participants self-reporting current ART use at PC24
- Treatment of zeros was added to accommodate this potential in subgroup analyses of HIV incidence.
- The community HIV prevalence covariate used to adjust the Step 1 HIV incidence analysis was further clarified to be a country-specific age and sex standardized HIV prevalence, using the age and sex distributions available from the Arm A and B intervention communities in Zambia and South Africa
- Clarification that Age will be computed from self-report or imputed birthdate, where birthday is imputed at 6 months prior to the visit date where age is reported.
- Addition of clarification that participants with a “sero-reversion” in their sequence of HIV status determinations will have all HIV visit status set to missing.
- Addition of unadjusted relative risk definition.
- Addition of analysis of the endpoint Viral Burden, as an indirect marker of the probability of exposure to an HIV-infected person with unsuppressed viral load.
- Change to include imputation in the primary analysis for missing data at PC12 visit for those enrolled and HIV-uninfected at PC0. This followed completion of blinded endpoint adjudication, after which it was determined that 11% of person time was omitted if the formerly proposed complete case approach was used. The complete cases analysis, excluding all person time with missing HIV status at PC12, will also be presented as a sensitivity analysis.
- Clarification that for seroconverters, if the first HIV-infected visit is an acute infection, the estimated time of infection will be the time of the visit with acute infection.



## C OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME

This section corresponds to the protocol (Version 1.0).



<b><u>Primary Outcome Measure</u></b>
•HIV incidence measured over 3 years in <b>Population Cohort</b>
<b><u>Secondary Outcome Measures</u></b>
<ul style="list-style-type: none"> <li>•<b>Population Cohort:</b> HIV incidence measured over 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> years, HSV-2 incidence, sexual risk behavior<sup>+</sup>, community VL<sup>+</sup>, viral suppression (ART patients)<sup>+</sup>, drug resistance (ART patients with detectable VL)<sup>+</sup></li> <li>•<b>Population Cohort and Health Center Data:</b> ART Adherence<sup>+</sup>, HIV disease progression and death<sup>+</sup>, ART toxicity<sup>+</sup>, HIV stigma<sup>+</sup></li> <li>•<b>Health Center Data:</b> TB notification and mortality rates</li> <li>•<b>Population Cohort, Health Center Data, CHiPs Data:</b> uptake of PMTCT<sup>+</sup>, uptake of male circumcision<sup>+</sup>, ART screening and uptake<sup>+</sup>, uptake of HIV testing and retesting<sup>+</sup>, time between diagnosis and initiation of care<sup>+</sup></li> </ul>
<sup>+</sup> Objectives that will also be addressed by the <i>Population Cross-Sectional Survey</i> , if funded
<sup>*</sup> Pending funding for these assays.

## D Analysis Cohorts of the Population Cohort

This section describes the analysis cohorts of the population cohort. For the purposes of analysis in the Population Cohort the beginning of the PopART intervention is defined as January 1, 2014.

Throughout, HIV status *by study testing* refers to the HIV testing conducted at site and central labs using the blood samples collected at the PC visits by the study nurse. It does not include HIV testing conducted by the CHiPs, or rapid HIV tests offered to PC participants during their PC visits.

### D.1 Population Cohort

The population cohort (PC) is all participants enrolled in the PC, including PC12N participants, enrolled in the second year at the PC12 visit and PC24 N participants enrolled in the third year at the PC24 visit.

#### D.1.1 Subgroups of the Population Cohort

An extended group of questions are administered to two subgroups at each PC round. The subgroups are mutually exclusive (so a participant is not asked to complete two extended sets of questions). The subgroups are re-selected each cycle.

- PC0, PC12, PC24 and PC36 Risk subgroups: A 20% randomly selected subgroup is given an extended sexual risk and stigma questionnaire.
- PC0, PC12, PC24 and PC36 Economics subgroups: A 20% randomly selected subgroup is given an extended economic and quality-of-life assessment.

### D.2 HIV Uninfected Cohort

The HIV Uninfected Cohort includes:

- PC participants who were negative at PC0 and/or PC12 and/or PC24 by study testing. Participants who are HIV-uninfected and enrolled at PC12N and PC24N are included.
- Determination of HIV status requires completed HIV testing according to the study HIV test algorithm, which generally requires a single, fourth-generation HIV test for HIV-uninfected status and two different fourth-generation tests for HIV-infected status. HIV status can also be determined by review of all available lab testing in consultation with the HPTN 071 endpoints committee.
- Participants who did not have HIV status determined as HIV-negative on at least one visit are not included in the cohort.

#### D.2.1 Subgroups of the HIV Uninfected Cohort

HIV uninfected cohorts for each year of the PC are defined as follows:

- **PC0, PC12, PC24, PC36:** All participants who have HIV status HIV-uninfected at the corresponding PC visit. These will include participants enrolled in PC12N, and PC24N.

### D.3 Primary Incidence Cohort

The primary endpoint analysis of HIV incidence will include HIV incidence evaluated in the second and third full year of the intervention as measured by the incidence at PC24 and PC36 visits amongst HIV uninfected PC0, PC12/PC12N and PC24/PC24N participants. Among these participants, the Primary Incidence Cohort includes the subset who meet the following criteria:

- PC0 participants who were negative at PC12 or, if PC12 HIV status is unknown, have subsequent HIV test status determined by study testing at PC24 and/or PC36.
- Participants who were HIV-uninfected when enrolled at PC12N and PC24N are included. Time on study will be from the earliest of PC12 or PC24 visit
- Determination of HIV status follows the description in Section D.2.
- HIV status was determined on at least two different visits, one of which was PC24 or PC36.
- Imputation will be used to include data from HIV negative PC0 participants with PC12 HIV status unknown who have HIV assessed at PC24 and/or PC36.

### ***D.3.1 Subgroups of the Primary Incidence Cohort***

HIV incidence cohorts for each year of the PC are defined as follows:

- **PC12:** All PC participants who have HIV status HIV-uninfected at PC12, including PC12N, and have HIV status determined in PC24. Imputation will be used for unknown HIV status at PC12, as above.
- **PC24:** All PC participants who have HIV status HIV-uninfected at PC24/PC24N, including PC24N, with HIV status determined in PC36. Imputation will be used for unknown HIV status at PC24, as above.

### ***D.3.2 Full Incidence Cohort***

The full incidence cohort includes HIV incidence evaluated in all years of follow-up of the PC as measured by the incidence at PC12, PC24 and PC36 visits amongst HIV uninfected PC0, PC12N and PC24N participants.

The full endpoint cohort follows the definition above, with the addition of

- PC0 participants who were negative at PC0 and had their last HIV status measured at PC12.

## **D.4 HIV-Infected Cohort**

All PC participants who have HIV-infected status at PC0, PC12, PC24, or PC36. Participant data are only included in the cohort from the date of the first HIV-infected visit.

### ***D.4.1 Subgroups of the HIV-Infected Cohort***

- **Seroconverter Cohort**  
All PC participants who acquire HIV infection during the HPTN071 protocol. A seroconverter is defined as a participant who has HIV-uninfected status documented at enrollment or during PC follow-up and subsequently has confirmed HIV-infected status. This includes participants who have acute HIV infection at the last study visit, without evidence of seroconversion (i.e., without detectable anti-HIV antibodies).
- **PC0, PC12, PC24, PC36**  
Participants of the HIV-Infected Cohort who are HIV infected at PC0, by study testing, at PC12, PC24, PC36, respectively
- **Community Viral Load: PC24**  
Viral load is measured in all HIV-infected participants at PC24, thus this eligible cohort is the same as HIV-infected PC24, above, minus those where viral load was not tested.  
**PC0, PC12 and PC36 Community Viral Load Random Sample**

Randomly selected subset of ~75 HIV-infected participants in each community in the HIV-infected cohort at PC0, PC12 and PC36. Seroconverters in the PC12 round are excluded from the sampling frame for PC12 cohort in the expedited evaluation of viral load for interim monitoring.

## D.5 Self-reported HIV-Infected Cohort

All PC participants who have self-reported they are HIV-infected at PC0, PC12, PC24, or PC36. Participants' data are included in the cohort from the visit they first self-report they are HIV-infected. In the case where participants did not consistently self-report HIV-infection and data are not assessed (e.g. current ART use is collected only when a participant self-reports HIV-infected), participants will be excluded from analyses requiring such data.

### D.5.1 Subgroups of the Self-reported HIV-Infected Cohort

- PC0, PC12, PC24, PC36  
Participants of the self-reported HIV-Infected Cohort who first report, or have previously reported, they are HIV-infected at PC0, PC12/PC12N, PC24/PC24N, PC36, respectively (each cohort includes those self-reporting HIV infected in previous visits).
- **Newly diagnosed after start of PopART:** all participants who self-report HIV-infected diagnosis after the initiation of PopART intervention (January 1, 2014).
- **Registered in care since start of PopART:** all HIV-infected participants who did not self-report being registered in care before the initiation of the PopART intervention who subsequently report being HIV-infected and registered in care.
- **Initiated ART since start of PopART:** All participants who did not self-report current ART before the initiation of the PopART intervention who subsequently report being HIV-infected and on ART during PC follow-up.

## E Variable definitions

Label	Description/Definition	Type	Units/Categories	Use in analysis
<b>Administrative</b>				
Household ID	Uniquely identifies each household randomly selected from the sampling frame	Label	8 digit number	Identifier
Participant ID	Uniquely identifies each selected participant	Label	10 digit number	Identifier
Barcode/specimen ID	Uniquely identifies specimens collected for each enrolled participant	Label	10-digit number	Identifier
Enrolled	Selected participant who consented to participate	Binary	Yes/No	Cohort
Triplet	Uniquely identifies each triplet	Label	1-7	Stratification
Randomization arm	Randomization arm for each community	Categorical	A,B,C	Primary covariate

Community number	Identifies community of each participant	Categorical	101-121	Cluster
Visit	Time point for data collection	Categorical	PC0, PC12, PC24, PC36	Study Time
Date of visit	Calendar date of visit	Calendar time	ddMMMy/PC0, PC12, PC24, PC36	
Duration on study	Duration between HIV tests: e.g. Date of PC12 specimen draw – Date of PC0 specimen draw in years	Duration	Years/ PC12, PC24, PC36	Time on study
<b>Laboratory Assessments</b>				
Site HIV Combo assay (HCA)	Singleton Architect HIV Ag/Ab Combo test (Abbott) HIV result from in-country (local lab) testing	Categorical	Reactive/Non-reactive PC0, PC12, PC24, PC36	Part of primary endpoint
LC HCA	Architect HIV Ag/Ab Combo test HIV result from LC. Performed as QC for 10% of site HCA nonreactive, and when site HCA is not done	Categorical	Reactive/Non-reactive PC0, PC12, PC24, PC36	Part of primary endpoint
LC Biorad HIV result	GS HIV Combo Ag/Ab EIA (BioRad) test HIV result from lab (LC) testing. Performed for all Site HCA reactive	Categorical	Reactive/Non-reactive PC0, PC12, PC24, PC36	Part of primary endpoint
LC within visit discrepancy result	Result of additional testing conducted by the LC when Reactive/non-reactive HIV discrepancy on two HIV tests from the same visit	Categorical	Negative/Positive/Inconclusive PC0, PC12, PC24, PC36	Part of primary endpoint
HIV confirmed status	Result determined by Site HCA, LC HCA, LC Biorad and any additional testing conducted by the LC. Additional testing is conducted at relevant visits for all participants who change HIV status between visits i.e. are potential seroconverters or who are observed to “sero-revert”	Categorical	Negative, Positive, Missing. PC0, PC12, PC24, PC36	Used to determine primary endpoint

Acute infection	Determination whether the first HIV-infected visit for a seroconverter was acute or not. Acute infections are characterized as confirmed infections without detection of antibodies	Categorical	Yes, No PC0, PC12, PC24, PC36	Used to characterize acute infection. Date of infection is estimated as acute visit date.
ARV drug testing	An objective, biomedical measure that detects an array of ARV drugs, if resources are available.	Yes/No	Presence/absence for each of an array of ARV drugs. Most probably assessed in HIV-infected PC24 cohort.	Objective marker of use of ART
<b>Demographics/Subgroups</b>				
Gender	Gender of participant	Categorical	Male/Female	Subgroups
Age in years at each visit	Age of participant at time of visit: calculated from birthdate and visit date. If exact birth date was unknown, is imputed as 6 months prior to the visit date where age in years was given.	Numeric	18 or older	Subgroups
Marital status, enrollment	Marital status at enrollment	Categorical	Currently married/living as married, never married, divorced/separated, widowed	Demographic
Education, enrollment	Education level at enrollment	Categorical	None/Grade 1-2, Grade 3-6, Grade 7-10, Grade 11-12, College/University, Other	Demographic
Sexually active at enrollment	Participant report of sexual activity at enrollment	Binary	Yes/No	Subgroups
HIV status at enrollment	HIV confirmed status at enrollment visit, PC0, PC12N or PC24N.	Categorical	Negative, Positive, Missing. Missing if no enrollment sample taken, or unable to determine	Subgroup

			HIV status at enrollment	
<b>Secondary Endpoints</b>				
HSV-2 status	Derived from the site and central HSV-2 results, Uninfected if site HSV-2 result was non-reactive. Infected if site testing was reactive. If local testing was gray zone or indeterminate, reactive or non-reactive as determined by central testing. Indeterminate if local gray zone and central test indeterminate i.	Categorical	Infected/Uninfected /Indeterminate. PC0, PC36	Secondary endpoint
Self-reported HIV status	Participant report of HIV status	Categorical	Skipped, Negative, Positive, Don't Know/Unwilling to disclose PC0, PC12, PC24, PC36.	Cohort
Plasma viral load	Number of viral copies per mL in plasma	Numeric or BLQ	Copies/mL or BLQ Subset of HIV-infected PC12, PC36 (75/community);PC24	Secondary endpoint
Undetectable PVL	Whether PVL is <400 copies/mL	Binary	0/1, subset of HIV-infected PC12, PC36 (75/community); PC24	Secondary endpoint
Self-reported ART uptake	Participant report of ART uptake, assessed only in those self-reporting HIV-infected status	Binary	Skipped, Yes/No PC0, PC12, PC24, PC36 (HIV-infected)	Secondary endpoint
Registered for HIV care	Participant report of registering for HIV care, assessed only in those self-reporting HIV-infected status	Binary	Skipped, Yes/No PC0, PC12, PC24, PC36 (HIV-infected)	Secondary endpoint
Date of most recent HIV care visit	Participant report of last clinic visit for HIV care	Calendar time	Skipped, MM/YY PC0, PC12, PC24, PC36 (HIV-infected)	Secondary endpoint

Number of sexual partners in prior year	Number of partners in last 12 months. 0 if no sexual partners in last 12 months	Count	0-999 PC0, PC12, PC24, PC36	Secondary endpoint
Number of sex events per month	Participant report of average number of sex events per month, assessed only in the cohort of participants assigned to the extended Risk questionnaire. 0 if no sexual partners in last 12 months	Count	0-99 PC0, PC12, PC24, PC36	Secondary endpoint for Risk subset
How often used condoms	Participant report of condom use, assessed only in the cohort of participants assigned to the extended Risk questionnaire	Categorical	Skipped, All the time /Sometimes/Never PC0, PC12, PC24, PC36	Secondary endpoint for Risk subset
Exchange of money/drugs/food/s helter for sex	Participant report of exchange of money, drugs, food or shelter for sex, assessed only in the cohort of participants assigned to the extended Risk questionnaire	Categorical	Yes/No PC0, PC12, PC24, PC36	Secondary endpoint for Risk subset
Any casual or one-time partners	Participant report of any casual or one-time partners. No if no sex partners	Categorical	Yes/No PC0, PC12, PC24, PC36	Secondary endpoint
Unprotected sex	Participant report that most recent sex act was unprotected. No if no sex partners	Categorical	Yes/No PC0, PC12, PC24, PC36	Secondary endpoint
Concurrent sexual partners	Participant report of concurrent sexual partners, assessed only in the extended Risk questionnaire. . No if no sex partners	Categorical	Yes/No PC0, PC12, PC24, PC36	Secondary endpoint for Risk subset
Inconsistent condom use	Participant report of any inconsistent condom use, assessed only in the extended Risk questionnaire	Categorical	Yes/No PC0, PC12, PC24, PC36	Secondary endpoint for Risk subset



HIV discordant relationship	Participant report of any partner with discordant HIV status, assessed only in the extended Risk questionnaire	Categorical	Yes/No PC0, PC12, PC24, PC36	Secondary endpoint for Risk subset
Stigma scores	HIV related stigma scores, calculated from 12 questions measured on a 4-point Likert scale, assessed only in the extended Risk questionnaire	Numeric	PC0, PC12, PC24, PC36	Secondary endpoint for Risk subset
Pregnancy during past year	Participant report of pregnancy during the past year	Categorical	Yes/No PC0, PC12, PC24, PC36 (Female)	Cohort
Use of ART for PMTCT during pregnancy	Participant report of ART use during pregnancy	Categorical	Yes/No PC0, PC12, PC24, PC36 (Female)	Secondary endpoint
Circumcision in the past year	Participant report of circumcision during the past year	Categorical	Yes/No PC0, PC12, PC24, PC36 (Male)	Secondary endpoint
Community level covariates				
HIV Prevalence at PC0	Proportion of tested cohort in each community who are HIV-infected	Numeric percentage	PC0	Subgroup
Age x gender x country standardized HIV prevalence at PC0	Estimate of proportion HIV-infected in each community, based on intervention data of 18—44 age and gender distribution in each country.	Numeric percentage	PC0	Primary adjustment variable

## F Baseline Tables and Study Conduct

### F.1 Description of tables for the Population Cohort

This section describes the tables of baseline characteristics of the PC0 cohort. A subset of these will be presented to the DSMB at each meeting. These tables will appear in the open DSMB report. When results are presented by study arm, as this is an unblinded trial, the arms will be labeled Arm A, B and C, corresponding to the trial arms.

Similar tables will describe the enrollment characteristics of the PC12N and PC24N cohorts. However, the PC0 cohort will comprise the primary description of the baseline characteristics of the communities prior to intervention.

### ***F.1.1 Study Accrual***

Activation dates, first enrollment dates, target accrual numbers, and the number of participants accrued each month are presented for each country and community.

### ***F.1.2 Baseline Demographic Characteristics***

Demographic characteristics summarized include age during PC0 recruitment, gender, education, marital status, employment status, type of employment among those currently employed, nights spent away from home in the last three months, and nights spent outside the community in the last three months. Characteristics are presented by country, community and arm for all participants and for men and women separately by country and community.

### ***F.1.3 Baseline Household Characteristics***

Household characteristics summarized include building type, main source of drinking water, and main source of energy used for cooking. Characteristics are summarized by country and arm.

### ***F.1.4 Baseline Risk Characteristics***

Risk characteristics summarized include alcohol use, recreational drug use in the last 12 months, sexual activity in the last 12 months, number of sex partners in the last 12 months, partners living outside the community and condom use during the last sex event for all participants. Circumcision status is reported for men. The number of sex partners in the last 12 months is categorized as 0, 1, 2 or 3 or more partners. Characteristics are summarized for all participants by country, community and arm and for men and women separately by country and community.

### ***F.1.5 Baseline Sexual Activity by Age Group***

Sexual activity risk characteristics are summarized by age group overall and for men and women separately. Risk characteristics summarized include reported sexual activity in the last 12 months, number of sex partners in the last 12 months, partners living outside the community and condom use during the last sex event.

### ***F.1.6 Baseline HIV Self-Report***

Self-reported HIV status and HIV testing history by country, arm and community are summarized for the entire cohort of enrolled participants and for the cohort of those participants who report no prior visits from CHIP teams on the date of enrolment to PC0. Self-reported HIV status is categorized as missing, positive, negative, unknown or unwilling to disclose, and never tested.

### ***F.1.7 Baseline Rapid Test Acceptance***

Baseline rapid test acceptance and rapid test results are presented by country, by arm, by arm in Zambia, by arm in South Africa and by community for the entire cohort of enrolled participants and for participants who report no prior visits from CHIP teams. Rapid tests refer to the HIV tests offered to the participant during the PC enrollment visit by the Research Nurse. The percentages of those accepting the rapid test are shown overall, for those self-reporting HIV- infected, for those self-reporting HIV-negative, and for those never tested. Each rapid test produces a result that is non-reactive, reactive or invalid. Per study procedure, a reactive rapid result is followed by a second rapid test. The “final” rapid result is reported in this table. The result is reported as non-reactive if the first test is non-reactive. The result is reported as reactive if both the first and second rapid tests are reactive. A reactive rapid result

followed by an invalid or non-reactive test, or not followed by a repeat test, is considered invalid/inconclusive. If the first rapid test is invalid, then the result is also considered invalid.

### ***F.1.8 Baseline HIV Care and ART Uptake***

Baseline HIV care and ART uptake among those self-reporting HIV-infected at baseline are summarized by country, arm and community. The number of self-reported HIV-infected participants who report that a CHiP team has not yet visited the household is shown. Participants who have been visited by a CHiP team and report a recent first positive HIV test may have discovered their HIV status through the study intervention. The year of the first positive HIV test and ever registering for HIV care are shown for all participants self-reporting HIV infected. The year registered for HIV care and ART use are summarized among those reporting registered for HIV care. The primary reason for starting ART, the year starting ART, and current ART use are summarized for those reporting ever using ART. Ever stopping ART in the last 12 months and missing any ART pills in the last seven days are summarized among those reporting current ART use.

### ***F.1.9 Baseline HIV and HSV-2 Results***

HIV and HSV-2 test results are presented by country, arm and community. HIV status is assessed by a combination of in-country and HPTN Laboratory Center (LC, Johns Hopkins) testing. A first HIV test is performed in-country. If the first test is non-reactive, the HIV test is considered negative (10% of these are retested at the LC for quality assurance). If the first test is reactive or invalid, a second test is conducted at the LC. In the case of discordant or inconclusive testing, the LC conducts further tests to establish HIV status. The percentages of the in-country HIV and HSV-2 test results are shown for those samples that have been tested. No result obtained refers to samples that were to be tested but could not be tested effectively due to machine failure, etc.

### ***F.1.10 Baseline HIV Prevalence***

Baseline HIV prevalence is presented for each community and overall. In addition, for men and women in each country separately, by age category, and by age category for each of men and women. The denominator for the prevalence calculations is the number with completed determination of HIV-status, including LC HIV confirmatory tests.

### ***F.1.11 Baseline HIV Care and ART Uptake Among HIV+***

Baseline HIV care and ART uptake are summarized among those HIV-infected by the in-country lab testing. Ever registered for HIV care is missing if the participant self-reported HIV-infected but did not answer the question, "Have you ever registered for HIV care?" None of those self-reporting something other than HIV-infected status are considered registered for care. Current ART use is missing if the participant self-reported HIV-infected but did not answer the question, "Have you ever taken any ART?" None of those self-reporting something other than HIV-infected status are considered on ART.

## **F.2 Study conduct measures**

### ***F.2.1 Consort Diagram***

A consort diagram will report for each arm both at the level of individual and community, following Consort diagram best practices for community randomized trials. The consort diagram will include reporting of new participants enrolled in PC12N and PC24N, and the number of participants retained in each PC round.

### **F.2.2 Retention and Enrollment at PC12N and PC24N**

In each PC round, retention of participants among those eligible for each PC round will be reported as completed, missed or terminated (or outcome not yet known, during the round). All those not terminated are eligible for the next PC round. The number of participants enrolled in PC12N and PC24N are added to those eligible for the next round.

### **F.2.3 Completeness of Specimen Collection**

In each PC round the completeness of specimen collection is presented by country, arm and community. Percentages of sample collection for in-country HIV testing, in-country HSV-2 testing, Laboratory Center (LC) testing and storage and in-country storage are summarized. The denominator for these participants includes all enrolled participants. Completeness of HIV testing

All specimens are tested for HIV using a singleton Architect run. All reactive HIV results by in-country testing will be confirmed at the HPTN Laboratory Center (LC) provided an aliquot for LC testing and storage was collected. Ten percent of the HIV non-reactive in-country results are selected for QA at the LC. The LC will also perform confirmatory testing for all samples for which the in-country testing did not yield a result. The percentages of the HIV confirmatory testing completeness and results from the LC are summarized.

## **G Blinding, Access to Data and Publication during the Study**

Neither site staff nor participants will be blind to community assignment. It is study policy not to report aggregate data by community name or have information about community arm assignment in public documents. And although only the DSMB and statisticians preparing analysis reports will review accumulating interim data by study arm, study sponsors, monitors and non-site staff are likely to become aware of community assignments while the study is ongoing. To the extent possible, however, decisions regarding additions or modifications to planned analyses, determination of inclusion in or exclusion from analysis cohorts or datasets, and rules for handling missing or incomplete data will be made by statisticians, study leadership or other study staff who do not have access to outcome data grouped by arm. Lab assessments will be done blinded to community treatment assignment and the Endpoints Committee will not be provided community assignments when adjudicating HIV endpoint data. The level of blinding maintained when performing these activities will be described in the study report or manuscripts, as relevant.

No data on comparisons between the intervention arms (A and B), nor between the intervention arms (A and B) and the standard of care arm (C), will be presented or published during the study.

The study team will publish and present data from the PC0 (baseline) data during the study. PC0 data will also be accessed by the mathematical modelling group to inform and validate the model.

## **H Interim Monitoring Guidelines**

### **H.1 Interim monitoring for Effect Size based on Intervention Uptake**

The uptake of intervention components will be reported using both data from the CHiPs (available only in arms A and B) and the population cohort (primarily through self-report). Targets have been set for each of the intervention components for CHiPs for Arms A and B. However, for interim monitoring, a

range of plausible intervention effect sizes will be assessed through mathematical models that allow for the combined effect of the prevention cascade.

### H.1.1 Protocol effect size

In the study design, mathematical models used the targets detailed in the Protocol (V1.0). These modelling results are included here for reference.

**Table 1- Parameter values assumed for the model of the impact of the intervention for central and optimistic target scenarios, and projected impact on HIV incidence in Arms A and B compared with Arm C, assuming intervention roll-out over a 6-month time period**

Parameter		Central Target		Optimistic Target	
Annual coverage of test and treat campaign		70%		75%	
Treatment failure & drop-out rate, per year		10%		10%	
Effectiveness of ART in blocking transmission		90%		95%	
Take up of male circumcision when offered		50%		50%	
		Arm A	Arm B	Arm A	Arm B
Zambia	Impact on cumulative incidence (3 years)	58%	25%	66%	29%
	Impact on cumulative incidence (2 first years)	54%	23%	62%	27%
	Impact on HIV incidence during Year 1	45%	19%	53%	23%
	Impact on HIV incidence during Year 2	63%	28%	72%	33%
	Impact on HIV incidence during Year 3	68%	31%	76%	36%
South Africa	Impact on cumulative incidence (3 years)	57%	23%	65%	27%
	Impact on cumulative incidence (2 first years)	52%	21%	61%	26%
	Impact on HIV incidence during Year 1	44%	18%	52%	23%
	Impact on HIV incidence during Year 2	62%	26%	71%	31%
	Impact on HIV incidence during Year 3	66%	29%	75%	33%

**Table 2- Parameter values assumed for the model of the impact of the intervention for central and optimistic target scenarios, and projected impact on HIV incidence in Arms A and B compared with Arm C, assuming intervention roll-out over a 12-month time period**

Parameter		Central Target		Optimistic Target	
Annual coverage of test and treat campaign		70%		75%	
Treatment failure & drop-out rate, per year		10%		10%	
Effectiveness of ART in blocking transmission		90%		95%	
Take up of male circumcision when offered		50%		50%	
		Arm A	Arm B	Arm A	Arm B
Zambia	Impact on cumulative incidence (3 years)	54%	23%	62%	27%
	Impact on cumulative incidence (2 first years)	47%	20%	56%	25%
	Impact on HIV incidence during Year 1	34%	14%	42%	19%
	Impact on HIV incidence during Year 2	61%	27%	70%	32%
	Impact on HIV incidence during Year 3	67%	31%	76%	36%

<b>South Africa</b>	Impact on cumulative incidence (3 years)	52%	21%	61%	26%
	Impact on cumulative incidence (2 first years)	46%	19%	54%	23%
	Impact on HIV incidence during Year 1	33%	14%	41%	18%
	Impact on HIV incidence during Year 2	60%	26%	69%	30%
	Impact on HIV incidence during Year 3	66%	29%	75%	33%

### **H.1.2 Interim modelling of effect size.**

The complexity of the multiple components of the intervention makes it difficult to estimate the population impact on HIV incidence. Operational futility in the study will use a mathematical model to assess the likely range of effect sizes, based on the intervention uptake data collected in the trial. The description of the mathematical model and the scenarios for uptake are detailed in a separate Modeling Projection Report. This will be used to estimate whether the power of the trial remains high.

The Study Team proposes that if the power for the comparison of Arms A and C under scenarios consistent with the observed intervention uptake becomes less than 50%, given data on HIV incidence in Arm C and HIV prevalence in the PC, the DSMB could recommend early stopping of the study for futility, i.e. when the trial is unlikely to have the power to demonstrate effectiveness.

Under current assumptions of 1% incidence and 22% HIV prevalence, 50% power corresponds to a PopART intervention community effectiveness of approximately 25%, i.e. a recommendation to stop the trial for futility if study power was estimated to be "only" 50% would correspond to stopping the trial if the effectiveness of Arm A relative to Arm C was projected to be smaller than 25%. At each DSMB meeting, updated projections of intervention effect and power based on updated assumptions and protocol changes will be provided in a separate Modeling Projections Report.

## **H.2 Interim monitoring of HIV incidence**

The study was powered assuming an HIV incidence rate of 1.0-1.5 per 100-person years, and an HIV prevalence of 15% in the population cohort of 2,500 per community, so 85% of the enrolled participants are HIV uninfected and are followed to measure HIV incidence. The between-community coefficient of variation of HIV incidence was assumed to be 0.15-0.20. The Protocol (v1.0) indicated that the study will be very well powered to detect an effect of 35% or larger in Arm A compared with Arm C, and moderately well powered to detect an effect of 30% under favorable assumptions. For the direct comparison of Arms A and B, the study will be well powered to detect a difference between effects of 60% and 30%, 55% and 25%, and 50% and 20%. The power calculations assume losses to follow-up of 20% over two years, and 25% over three years.

During the trial, power estimates will be updated based on information available from the PCO and the modelled projections of effect size. These details will be provided in document that will be updated for each DSMB review when information changes.

Expected information that will require updating of power assumptions:

- Prevalence: The prevalence in PCO will be available to assess the prevalence assumptions shortly after PCO is complete.
- Between community variance of HIV incidence: the between-community variance of HIV prevalence is expected to be a good approximation to check this assumption. This will be available shortly after PCO is complete.

- Arm C incidence: HIV incidence from the PC12 cohort can be used to assess the incidence assumption and assess the power assumptions of the study.
- Loss to follow-up: 20% over two years, and 25% over three years
- Effectiveness: Interim assessment of effectiveness by comparison of emerging data on HIV incidence is not planned. Because full intervention scale-up will not be achieved prior to PC12, HIV incidence comparisons at PC12 are unlikely to reflect a significant change. The HIV incidence from PC24 will be completed too late in the study to be useful as an interim assessment. Instead, the modelling group will estimate potential effectiveness using data from intervention uptake and PC0.

### **H.3 Interim Evaluation of Viral Load Suppression**

The PopART test-and-treat intervention relies for its effectiveness on diagnosing a large proportion of HIV-infected individuals in the community, linking them to care, starting them on ART as soon as possible and maintaining high levels of retention, adherence and viral suppression. All the steps in this cascade are monitored continuously during the delivery of the intervention, primarily using process data. We will also monitor viral suppression in the *Population Cohort* across all study arms at PC12, where viral suppression at PC12 may provide an early warning of any major deficiencies in delivery so that corrective action could be taken at an early stage.

#### ***H.3.1 Expedited PC12 viral load testing and assessment of community viral load***

Expedited PC12 viral load testing in the Population Cohort will be used as a monitoring tool to inform corrective action in the HPTN 071 (PopART) trial. At the PC12 visit, the majority of HIV-infected patients starting on ART since the start of the intervention in Arms A and B (including those starting outside national guidelines) will have been on ART for 3-12 months, allowing for the time needed for testing and linkage to take place. Data on viral suppression among these patients will provide an early indication of treatment adequacy. Carrying out the 12-month viral load testing, expedited to inform interim monitoring, will allow early corrective action to be taken if needed, while not requiring the addition of any further testing as it is already planned as a secondary trial outcome.

The main assessment of viral load suppression will occur at the PC24 follow-up when most patients will have been on ART for 1-2 years. For this reason, the trial protocol sets this time-point as the most relevant for assessing viral suppression and will conduct viral testing in *all* HIV-infected participants. The larger sample size at 24 months will provide greater power and precision. Expediting PC24 month viral load testing for more immediate availability of results is not proposed, since the complete results are unlikely to be available with enough time to deploy corrective action. For example, if viral load results are available within 3 months of the last PC24 specimen being collected, the final round of follow-up (PC36) will already be underway before any corrective action could be taken. However, if the PC12 survey were to indicate reasons for concern, expedited testing at 24 months could be reconsidered.

Note that as specified in the Expedited PC12 viral load testing plan, the protocol team leadership will have full access to the VL data set among the subset of participants who self-reported being on ART at PC0 or PC12.

#### ***H.3.2 ARV drug testing***

An objective, biomedical measure of ARV drug use may be used to define “on ART”. An affordable and efficient assay that detects an array of ARV drugs is available at the LC and we propose using this in combination with self-report if resources are available. Assessments of the correspondence between self-report and detection of ARV in samples will be used to judge the accuracy, and thus the use, of self-report in analysis. Funding for this assessment is not yet secured, however options for use of this

biomarker are included in the SAP. If ARV testing is performed, it would likely be performed for participants who are HIV-infected at PC24, using samples from the PC24 visit.

### **H.3.3 PC12 VLS Cohort**

A random sample of 100 participants from the PC0 HIV-infected cohort will be selected per community to achieve a target sample size for expedited testing at PC12 of 75 per community, allowing loss to follow-up between PC0 and PC12, inadequate samples, processing errors and other deficiencies.

#### **Analysis cohorts:**

##### **1. PC0 HIV-infected**

All sampled P0 HIV-infected participants with VL results. This larger cohort will have greater precision for overall rate of VLS

##### **2. PC0 HIV-infected and PC12 self-reported HIV-infected on ARVs at PC0 or PC12 visit.**

Option 1 (Self-report only ): The subset of sampled PC0 HIV-infected participants who self-report current ARV use in PC0 and/or PC12. This cohort will be used to assess ART adherence.

Option 2 (Self report or biomarker): The subset of sampled PC0 HIV-infected participants who either have ARV's detected in their plasma sample or self-report current ARV use in PC0 and/or PC12.

### **H.3.4 Blinding to interim viral load results**

While the study team will remain blinded to overall community viral load, they will have access to the PC 12 VL data on those on ART, in order that corrective action can be taken if necessary.

### **H.3.5 Power for comparisons in PC12 expedited VLS**

The table shows the expected sample size for viral load testing at each visit in Arm A, by country. It also shows the expected precision of the estimated proportion of patients virally suppressed, assuming an underlying rate of 90%. The table assumes that the main interest is in testing for viral suppression among patients who have been on ART at any time during the follow-up period, including those already on ART at baseline (assumed to be around 25% of HIV-infected on average) as well as those started on ART following the start of the intervention (assumed to be 70% of HIV-infected not already on ART at baseline).

The available sample size will provide a precise measure of PC12 viral suppression overall and for Zambia and S Africa separately. It will also give an early indication of gross under-performance in any one cluster. For example, if viral suppression in one cluster is as low as 60%, the precision on this estimate will be  $\pm 12.6\%$  so we would be able to say reliably that this cluster is not reaching a target of (say) 75% or 80%. The corresponding estimates are provided for Arms B and C. Because numbers on ART in each cluster will be somewhat lower than in Arm A, the precision of the viral suppression estimates will be correspondingly lower. However, we consider that these estimates are sufficiently precise for the purposes of this monitoring exercise.

#### **Estimated sample size and precision for PC12 VLS**

<b>Arm A</b>			
<b>Visit</b>	<b>HIV positive tested for VL</b>	<b>Number on ART<sup>1</sup></b>	<b>Precision of proportion virally suppressed<sup>2</sup></b>
12m			
Per triplet	75	58	$\pm 7.7\%$
Total (7 triplets)	525	406	$\pm 2.9\%$



Zambia (4 triplets)	300	232	± 3.9%
S Africa (3 triplets)	225	174	± 4.5%
<b>Arm B</b>			
12m			
Per triplet	75	44	±8.9 %
Total (7 triplets)	525	308	±3.4 %
Zambia (4 triplets)	300	176	±4.4 %
S Africa (3 triplets)	225	132	±5.1 %
<b>Arm C</b>			
12m			
Per triplet	75	36	±9.8 %
Total (7 triplets)	525	252	±3.7 %
Zambia (4 triplets)	300	144	±4.9 %
S Africa (3 triplets)	225	108	±5.7 %

<sup>1</sup> Assumes 25% already on ART at baseline and 70% of those not on ART are diagnosed and started on ART

<sup>2</sup> 95% CI for proportion virally suppressed among those on ART, assuming estimated proportion is 90%. These CI do not account for clustering due to the community randomized design.

### **H.3.6 Ethical issues and anonymization**

The protocol states that results from viral load testing in the *Population Cohort* will not be fed back to participants (e.g. if failure of viral suppression is found). Doing so would provide a different level of service for these PC patients and could distort the findings of the trial, leading to Hawthorne effects in the *Population Cohort*. Also, in most cases laboratory results will only be available after a long delay, diminishing the clinical relevance of these results. Local health authorities and implementing partners could still be informed of community trends which could facilitate efforts to explore and implement changes at the community service level, in order to benefit all patients in a given community.

Specimens could be anonymized (specimen identification (ID) number de-linked from PC ID number) before going forward for viral load testing. This would remove the ethical dilemma that would otherwise exist. However, delinking these expedited viral load data from other data on *Population Cohort* participants would preclude further statistical analysis of trends in viral load over time and related socio-demographic and other risk factors, and so we are not proposing this at this time.

# I Statistical Analyses

This section describes the statistical analyses of the primary and secondary outcomes that will be conducted on enrolled participants in the population cohort and the analysis of the intervention data from the CHiPs

PC data is collected in all communities; thus, analyses include all three arms of the trial. CHiPs data is collected only in the interventions communities, thus analyses include only Arms A and B.

## I.1 Descriptive Analyses

### I.1.1 By community

Within each community, summary statistics (e.g., frequencies, percentages, means, medians, inter-quartile range, minima and maxima) that are appropriate to the measurement scale will be used to describe demographic, behavioral, HIV testing and medical history and ART use data. Continuous variables may be described using categorical levels chosen based on previous experience with similar studies; depending on the final distributions of these variables and providing it does not meaningfully impact the intent of analyses based on them, these categories may be modified prior to final report to allow better characterization of the relevant distributions.

### I.1.2 By arm

Different descriptive summaries will be computed as appropriate to the analysis questions.

1. Participant aggregated: Summary statistics are computed treating the participants as a single group, i.e., for the  $i^{th}$  community ( $i = 1, 2, 3$ ) in the  $j^{th}$  triplet ( $j = 1 \dots 7$ ), with  $N_{ij}$  individuals ( $k = 1 \dots N_{ij}$ ), where we assume that  $i$  indexes the communities in arms A ( $i = 1$ ), B ( $i = 2$ ) and C ( $i = 3$ ) respectively

$$\bar{y}_i = \frac{1}{\sum_j N_{ij}} \sum_{jk} y_{ijk}$$

Standard errors and confidence limits will not be provided for participant aggregated summaries.

2. Community aggregated: Summary statistics are computed by summarizing the within community summaries by arm. E.g.

$$\bar{y}_i = \frac{1}{7} \sum_j \bar{y}_{ij} = \frac{1}{7} \sum_j \frac{1}{N_{ij}} \sum_k y_{ijk}$$

Standard errors and confidence limits for community aggregate estimates will be computed using the within group sample variance of cluster means

$$S_i^2 = \frac{\sum_{j=1}^7 (\bar{y}_{ij} - \bar{y}_i)^2}{6}$$

Note: Participant and community aggregated summaries are expected to be similar when the number of people in each community (sub) population are similar. By the design of the study it is intended that the overall number of people in each community is similar.

3. Descriptive matched differences across arms: Summary statistics are computed within each community, and appropriate comparative statistics are computed within matched pairs and summarized across the 7 pairs. The computation is repeated for each pair of arms.

- Difference in means:

For each triplet and arms A (i = 1) and C (i = 3), for example: compute the jth triplet specific difference in means:  $d_j^{AC} = \bar{y}_{1j} - \bar{y}_{3j}$ ; the average difference in means between arms is

$$D^{AC} = \frac{1}{7} \sum_{j=1}^7 d_j$$

- Risk ratio

For each triplet and arms A and C, for example: compute the triplet specific relative risk ratio:  $r_j^{AC} = \frac{p_{1j}}{p_{3j}}$ . The summary statistic is the geometric mean of the relative risks:

$$R^{AC} = \exp(\bar{s}^{AC}) = \exp\left(\frac{\sum s_j^{AC}}{7}\right)$$

where  $s_j^{AC} = \log(r_j^{AC})$

- Rate ratio

For each triplet: compute the triplet specific rate ratio:  $r_j^{AC} = \frac{r_{1j}}{r_{3j}}$  where  $\bar{r}_{ij} = \frac{1}{\sum_k t_{ijk}} \sum_k y_{ijk}$  with  $t_{ijk}$  = time on study and  $y_{ijk} = 1$  if event is observed, 0 otherwise. The summary statistic is the geometric mean of the relative risks:

$$R^{AC} = \exp(\bar{s}^{AC}) = \exp\left(\frac{\sum s_j^{AC}}{7}\right)$$

where  $s_j^{AC} = \log(r_j^{AC})$

- Odds ratios

For each triplet and arms A and C, for example: compute the triplet specific odds ratio  $r_j^{AC} = \frac{p_{1j}(1-p_{3j})}{p_{3j}(1-p_{1j})}$ . The summary statistic is the geometric mean of the relative risks:

$$R^{AC} = \exp(\bar{s}^{AC}) = \exp\left(\frac{\sum s_j^{AC}}{7}\right)$$

where  $s_j^{AC} = \log(r_j^{AC})$

## I.2 Primary Analysis

### I.2.1 HIV Incidence

**Question: Does the PopART intervention reduce risk of HIV acquisition?**

Endpoint: Incident HIV infection

Cohort: Primary Incidence Cohort

Secondary cohort: Full Incidence Cohort

Details:

Determination of incident HIV infections will be determined using site and LC HIV testing, with an algorithm followed for additional testing to confirm HIV infection status, as described in the **Procedures for HPTN 071 primary endpoint review**. Any cases with non-conforming test results will be adjudicated by the Virology Endpoint Adjudication Committee, using the **HPTN 071 Adjudication plan**.

Incident HIV infection will be assessed approximately annually as each PC round is conducted and will be used as the primary endpoint for the intervention effect. Individuals who drop out of the study and

refuse further testing prior to completion of follow-up and individuals who die prior to completion of follow-up will be treated as uninformatively censored as of their last valid HIV status determination. Visits are only included if HIV status was assessed by study HIV testing. Participants enrolled in PC12N and PC24N, after the onset of the intervention, are assumed to contribute to assessment of intervention effectiveness in the same way as those enrolled in PC0.

Person years of follow-up are calculated as:

1. The time between each PC visit and the next subsequent visit (i.e. PC0 to PC12, PC12/PC12N to PC24 and PC24/PC24N to PC36) for participants who are HIV negative at their initial visit. Only visits where HIV status was determined are included.
2. The time between last HIV-negative visit and the estimated seroconversion date for participants who seroconverted. Estimated seroconversion date is defined as the date halfway between the last negative HIV test result and the first HIV infected test result where the first infected visit is not acute. If the first infected visit is acute, the estimated seroconversion date is defined as the observed visit date at which the acute infection was detected.
3. Each participant contributes person years for each pair of visits with HIV testing.

Seroconverters are participants in the cohort who were HIV uninfected by study testing at PC0, PC12, PC12N, PC24 or PC24N and who subsequently are HIV infected by study testing at PC12, PC24 or PC36. Any participant who has a known sample mix-up, evidenced by a visit with confirmed HIV-infection followed by a visit with confirmed HIV-negative status, is omitted from the analysis.

**Age and Sex:** Sex is assigned to each person as most recently reported during study follow-up. Age group is assigned to each record using a Lexis expansion for age-at-risk adjustment (i.e. age reassessed during each portion of an observed time period) , based on the reported or estimated birthdate, and the visit dates in each round for each participant.

**Descriptive analysis:** The number of events and total person years, HIV incidence rates and 95% confidence intervals will be presented for each community, with 95% confidence intervals based on the Normal approximation to the Poisson distribution. The same data will also be presented for each community for men and women separately; by age categories; by age for men and women.

The by arm summary will be computed by combining the incidence data for each community with a log transformation applied to reduce skewness. The geometric mean and associated 95% CI will be calculated for each of the three trial arms, and also separately for each arm by country. Unadjusted relative risk ratios, prevalence ratios, and rate ratios will be reported as the ratios of unadjusted geometric means across arms; confidence limits will be based on the residual MSE of an ANOVA with triplet and arm, on the log-transformed risks/prevalences/rates, using a  $t$  distribution statistic with 12 degrees of freedom. (Note: this is identical to the Step 2 analysis below, conducted on the community incidence rates.)

**Analysis:** A two-stage analysis will be used. In the first stage, we estimate the expected number of events in each community based on age, gender and triplet for all three arms simultaneously. In the second stage, we conduct a formal statistical comparison for differences in observed versus expected incidence by arm for the primary comparison between Arm A and C. A two-sided test with  $\alpha = .05$  will be used. Arm B versus C and Arm A versus B will also be compared, using a two-sided test with  $\alpha = .05$ .

Analyses will not be weighted to account for the sampling design or the lost to follow-up (i.e. selection of one person per household and non-response). No adjustment is planned for multiple comparisons.

**Details for two-stage analysis of incidence outcomes.**

To compute incidence, the number of seroconversions in each community is divided by the person-years of follow-up for that community.

**Stage 1:**

1. Poisson regression will be used to adjust for confounding variables at the individual level. The model will be fitted using data from all three arms, prior to comparisons for specific arms under comparison. The regression model will include terms for the covariates of interest and triplet but not trial arm.

$$\log(I_{ijk_m}) = \alpha_j + \beta h_{ij} + \sum_l \gamma_l z_{ijk_{ml}}$$

where  $I_{ijk_m}$  is the indicator of incidence for the  $k^{th}$  individual's  $m^{th}$  (partial) year ( $k = 1...N_{ij}$ ) in the  $j^{th}$  study triplet ( $j = 1...7$ ) and  $i^{th}$  study arm ( $i = 1,2,3$ ),  $h_{ij}$  is age and sex standardized baseline HIV prevalence in the  $i,j^{th}$  community and  $z_{ijk_{ml}}$  is  $l^{th}$  covariate.

Individual level covariates to be used for adjustment are:

- a) Age during each portion of an observed time period in groups (18-24, 25-29, 30-34, 35-39, 40+) – Age category can change during each year of follow-up
- b) Sex
- c) Age x Sex interaction

Community-level covariate to be used for adjustment is age and sex standardized HIV prevalence at baseline. The degrees of freedom in the paired t-test will be reduced by 1 to account for this covariate.

2. A fitted model will be used to obtain the ratio of observed-to-expected (O/E) events, and a log transformation will be applied to this ratio (the log ratio-residual). The expected number of events in the  $i^{th}$  arm of the  $j^{th}$  triplet is calculated as:

$$e_{ij} = \sum_{k_m} t_{ijk_m} \hat{I}_{ijk_m} = \sum_{k_m} t_{ijk_m} \times \exp\left(\hat{\alpha}_j + \hat{\beta} h_{ij} + \sum_l \hat{\gamma}_l z_{ijk_{ml}}\right)$$

Where  $t_{ijk_m}$  is the person years contributed in the  $m^{th}$  (partial) year for the  $k^{th}$  individual.

3. The adjusted rate ratio for the  $j^{th}$  triplet for arms  $i_0$  and  $i_1$  is calculated as:

$$\hat{\theta}_j(i_0, i_1) = \frac{d_{i_0j}/e_{i_0j}}{d_{i_1j}/e_{i_1j}}$$

where  $d_{ij}$  is the observed number of events.

**Stage 2:**

1. Take the logarithm of the adjusted rate ratio:

$$h_j(i_0, i_1) = \log\left(\hat{\theta}_j(i_0, i_1)\right)$$

Take the mean over triplets to get the log intervention effect (the mean log adjusted rate ratio):

$$\bar{h}(i_0, i_1) = \sum h_j(i_0, i_1) / 7$$

The point estimate of the intervention effect comparing arms  $i_0$  and  $i_1$  is the geometric mean of the adjusted rate ratios  $R_{i_0 i_1} = \exp(\bar{h}(i_0, i_1))$

2. Conduct a two-way ANOVA on the log ratio-residuals, using triplet and arm, which is the three-arm extension of a paired t-test: The residual MSE, which has 11 degrees of freedom, is used to compute the empirical standard error of the log intervention effect (mean pairwise difference in log ratio-residuals) between arms

$$s_d = \sqrt{\frac{2 \times \text{MSE}}{7}}$$

3. Carry out paired t-test on pairwise log adjusted rate ratios

$$t(i_0, i_1) = \frac{\bar{h}(i_0, i_1)}{s_d}$$

The p-value of  $t(i_0, i_1)$  is assessed assuming a  $t$  distribution statistic with 11 degrees of freedom and will be used to assess the strength of evidence against the null hypothesis

4. Confidence interval for the log adjusted rate ratio are computed as:

$$\bar{h}(i_0, i_1) \pm t_{11, 0.025} \times s_d$$

### Imputation of HIV infection assessment at PC12

A substantial proportion of the person years between PC12 and PC36 would be omitted because of the number of persons who do not have HIV status assessed at PC12 (either because of missed visits or because a specimen was not collected) but have known HIV status at a later visit (PC24 and PC36). Imputation methods will be used to include these person years and endpoints in the primary analysis. For participants who change serostatus, i.e. HIV-negative at PC0, missing results at PC12 and HIV-positive at PC24 (or also missing PC24 and HIV-positive at PC36), PC12 **HIV status** is imputed for the PC12 visit only. For HIV-negative participants, i.e. HIV-negative at PC0, missing PC12, HIV-negative at PC24 (or missing PC24 and HIV-negative at PC36), HIV serostatus is known to be HIV-negative. It is not necessary for the primary analysis to impute missing PC24 data, since having HIV status at PC12 and PC36 is sufficient to be included in the primary analysis. **Specimen collection date** for PC12 will be estimated as the mean relative proportion of time between visits for all persons from the same community with visits at PC0, PC12 and PC24.

For example, the specimen collection date,  $t_{ijn}^{(12)}$  for the nth participant in arm i, triplet j is estimated as:

$$t_{ijn}^{(12)} = t_{ijn}^{(0)} + \frac{\bar{t}_{ij.}^{(12)} - \bar{t}_{ij.}^{(0)}}{\bar{t}_{ij.}^{(24)} - \bar{t}_{ij.}^{(0)}} (t_{ijn}^{(24)} - t_{ijn}^{(0)})$$

where  $\bar{t}_{ij.}^{(k)}$  is the mean specimen collection date for all such participants in arm i, triplet j and visit k.

These are the patterns where imputation will occur:

- a) Seroconverters

PC0	PC12	PC24	PC36
N	.	P	P

	N	.	P	.
	N	.	.	P
b) Negatives				
	N	.	N	N
	N	.	N	P
	N	.	N	.
	N	.	.	N

The sero-status imputation method is an “adjustment cells hot-deck” approach. For any participant needing sero-status imputation, we select a “donor” at random with replacement from the adjustment pool, defined as all participants from a) the same community (therefore the same arm) and sex b) not missing PC12 HIV status and c) with testing that matches the observed test results of the participant, excepting the missed PC12 visit. HIV status at PC12 is assigned using the donor value. Visit time is a cell mean imputation, computed in two steps: 1) the mean fractional time between visits is computed for the corresponding community 2) visit time for PC12 is computed using that mean fraction time between the observed participant visits.

### Primary analysis, with imputation of missing PC12 data

Twenty imputation data sets will be constructed. The two-step primary analysis will be repeated for each dataset, producing 20 estimates of the logarithm of the adjusted rate ratios for each pair of arms and the corresponding ANOVA based MSE. The primary analysis estimates will be the average of the m = 1...20 estimates over the imputation datasets:

$$\hat{h}_{\text{imp}}(i_0, i_1) = \frac{1}{M} \sum_{m=1}^M \hat{h}_m(i_0, i_1)$$

Where  $\hat{h}_m(i_0, i_1)$  is the log intervention effect (of Arm  $i_1$  compared to Arm  $i_0$ ) for the mth imputation. The variance,  $\hat{V}_{\text{imp}}$ , for the primary analysis test statistic will combine the variance for each of the 20 imputed datasets, and the variation in the adjusted rate ratio across the 20 imputed datasets, using standard imputation methods. That is, for M imputations

$$\hat{V}_{\text{imp}} = \hat{U}_M + \frac{M+1}{M} \hat{B}_M$$

where

$\hat{U}_M = \frac{1}{M} \sum_{m=1}^M \hat{U}_m =$  within-imputation variance of the pairwise comparisons across arms, where  $\hat{U}_m = \frac{2}{7} MSE_m$  for the mth imputation, and

$$\hat{B}_M = \frac{1}{(M-1)(3-1)} \sum_{m=1}^M \left( h_m(1,2) - h.(1,2) - h_m(.,.) + h.(.,.) \right)^2 + \left( h_m(1,3) - h.(1,3) - h_m(.,.) + h.(.,.) \right)^2 + \left( h_m(2,3) - h.(2,3) - h_m(.,.) + h.(.,.) \right)^2 + \quad = \text{between imputation}$$

variability in the estimates of intervention effects. (Notation: “.” Implies average over that index, so  $h.(1,2)$  is an average over all the imputation estimates of the intervention effect for arms 1 and 2, and  $h_m(.,.)$  is an average over the three pairwise estimates for imputation m.) This is essentially the MSE of a two-way ANOVA of M imputations with factors imputation and pairwise comparison.

Following the primary analysis above, the paired t-test on log adjusted rate ratios for arms  $i_0, i_1$  is:

$$t_{imp}(i_0, i_1) = \frac{\hat{h}_{imp}(i_0, i_1)}{\sqrt{\hat{V}_{imp}}}$$

The p-value of  $t_{imp}(i_0, i_1)$  is assessed assuming a  $t$  distribution statistic with 11 degrees of freedom and will be used to assess the strength of evidence against the null hypothesis.

### **1.2.2 Subgroup analysis**

The analysis of HIV risk will be conducted for the following subgroups:

1. Men and women
2. Person years for younger and older (<25, ≥25 yo)
3. Person years from Younger men, Older men, Younger women, Older women

The analysis approach will follow the primary analysis of HIV risk.

#### **Treatment of zeros**

If in any subgroup analysis there is a community with 0 eligible participants, the triplet with that community will be omitted from the analysis.

If there is a community with at least one eligible participant, but 0 events, 0.5 will be added to the number of events and the number of participants for all communities in that triplet at the first stage of the analysis.

### **1.2.3 Supportive analyses**

#### **1. Entire Intervention Period**

The primary analysis will be repeated using all the follow-up time in the Full Incidence Cohort (i.e. including the first year of the PC follow-up).

#### **2. Intervention effect by Year**

Intervention effectiveness will be assessed for each year of PC follow-up. Imputation will be used at both PC12 and PC24 for participants with a prior HIV-negative assessment, who did not have an HIV status assessed at PC12 and/or PC24.

#### **3. Complete case analysis, excluding participants not assessed for HIV in PC12**

A complete case analysis will be reported, that excludes all person years and events that occur with no direct assessment of HIV status at PC12, that is, without the use of imputation.

#### **4. Permutation test**

Evidence for the intervention effectiveness will also be assessed using a non-parametric permutation test. The analysis above will be recomputed for all possible randomizations that were computed at the beginning of the trial under the restricted randomization scheme. The number of allocations  $n$  for which the incidence rate ratio is as extreme as the value observed in the trial will be counted and a 2-sided p-value will be calculated as  $n$  divided by the total number of possible allocations.



## I.3 Interim Monitoring Analysis

### I.3.1 Viral Load Suppression

**Question:** For HIV-infected participants on ART, is the proportion virally suppressed lower in Arms A and B compared to C?

**Question:** For HIV-infected participants is the proportion virally suppressed high, and is it higher in Arm A and B compared to C?

**Endpoint:** HIV plasma viral load is suppressed (PVL < 400 copies/mL)

**Cohort:**

1. Random subset of PC12 samples selected from the PC0 HIV-infected Cohort
2. Subset of above restricted to HIV-infected on ART by self-report at either PC0 or PC12 (or lab-based assay, if funding permits)

**Descriptive analysis:** For each cohort, the number in the cohort, the number and proportion virally suppressed will be reported for each community, and for each arm (community-aggregated), with 95% confidence limits for community aggregated summaries as previously defined. The characteristics of (log) viral load in each community will be presented: mean, median, SE, range

The by arm summary will be computed by combining the individual proportion or mean for each community with a log transformation applied to the plasma viral load values to reduce skewness. The geometric mean and associated 95% CI will be calculated for each of the three trial arms, and also separately for each arm by country.

**Analysis:** The statistical analysis for both questions compares the proportion virally suppressed using an unadjusted cluster-based analysis of the relevant cohort selected for evaluation.

1. The prevalence ratio for each triplet is calculated as:

$$r_j(i_0, i_1) = \frac{p_{i_0j}}{p_{i_1j}}$$

where  $p_{ij}$  is the observed prevalence of events in the  $j^{\text{th}}$  triplet for arm  $i$ .

2. Take the logarithm of the prevalence ratios:

$$s_j(i_0, i_1) = \log(r_j(i_0, i_1))$$

The point estimate of the intervention effect comparing arms  $i_0$  and  $i_1$  is the geometric mean of the prevalence ratios  $R_{i_0i_1} = \exp(\bar{s}(i_0, i_1)) = \exp\left(\frac{\sum s_j(i_0, i_1)}{7}\right)$

3. Compute a confidence interval for the mean log prevalence ratio:

$$\bar{s}(i_0, i_1) \pm t_{12, 0.025} \times s_d$$

where  $s_d$  is the empirical standard error for mean pairwise difference based on the MSE of the two-way ANOVA of the (log) prevalence ratios from the 21 communities fitted by triplet and arm.

## I.4 Secondary Objectives: Population Cohort

### I.4.1 Community Viral Load at PC24

**Question:** Does the PopART intervention reduce community viral load?

**Endpoint:** HIV plasma viral load is suppressed (PVL < 400 copies/mL)

**Cohort:** PC24 HIV-infected Cohort

**Descriptive analysis:** The number in the cohort, and the number and proportion virally suppressed will be reported for each community, and for each arm (participant-aggregated), with 95% confidence limits based on the binomial distribution. The characteristics of (log) viral load in each community will be presented: mean, median, SE, range.

The by arm summary will be computed by combining the proportion or mean for each community with a log transformation applied to reduce skewness. The geometric mean and associated 95% CI will be calculated for each of the three trial arms, and also separately for each arm by country.

**Analysis:** A two-stage analysis will be used. In the first stage, we estimate the expected proportion with viral suppression in each triplet and arm for all three arms simultaneously. In the second stage, we conduct a formal statistical comparison for the primary comparison between Arm A and C. A two-sided significance test, and the corresponding 95% confidence interval will be used to assess the evidence against the null hypothesis. Significance tests and 95% confidence limits will also be presented for Arm B versus C and Arm A versus B.

### Details for two-stage analysis of proportions

The proportion virally suppressed in each community is the proportion in the cohort with PVL < 400.

Stage 1:

1. Logistic regression will be used to adjust for confounding variables at the individual level. The regression model will include terms for the covariates of interest and triplet but not trial arm.

$$\text{logit}(y_{ijk}) = \alpha_j + \sum_l \gamma_l z_{ijkl}$$

where  $y_{ijk}$  is the binary indicator of suppressed viral load,  $i$  is  $i^{\text{th}}$  study arm ( $i = 1,2,3$ ),  $j$  is  $j^{\text{th}}$  study triplet ( $j = 1 \dots 7$ ),  $k$  is  $k^{\text{th}}$  individual ( $k = 1 \dots N_{ij}$ ) and  $z_{ijkl}$  is the covariate value for the  $l^{\text{th}}$  covariate.

Individual level covariates to be used for adjustment are:

- a) Age at PC24 visit in groups (18-24, 25-29, 30-34, 35-39, 40+)
  - b) Sex
  - c) Age x Sex interaction
2. A fitted model will be used to obtain the ratio of observed (O) to expected (P) proportions, and a log transformation will be applied to this ratio-residual. The expected proportion in the  $i^{\text{th}}$  triplet of the  $j^{\text{th}}$  study arm is calculated as:

$$p_{ij} = \sum_k \hat{y}_{ijk} = \sum_k \frac{\exp(\hat{\alpha}_j + \sum_l \hat{\gamma}_l z_{ijkl})}{1 + \exp(\hat{\alpha}_j + \sum_l \hat{\gamma}_l z_{ijkl})}$$

3. The ratio-residual for the  $j^{\text{th}}$  triplet of the  $i^{\text{th}}$  study arm is calculated as:

$$R_{ij} = \frac{o_{ij}}{p_{ij}}$$

where  $o_{ij}$  is the observed proportion of events in the  $i^{\text{th}}$  arm of the  $j^{\text{th}}$  triplet. The adjusted risk ratio for each triplet for arms  $i_0$  and  $i_1$  is calculated as:

$$\rho_j(i_0, i_1) = \frac{R_{i_0j}}{R_{i_1j}}$$

Stage 2:

4. Take the logarithm of the adjusted risk ratios:

$$d_j(i_0, i_1) = \log(\rho_j(i_0, i_1))$$

The point estimate of the intervention risk ratio comparing arms  $i_0$  and  $i_1$  is the geometric mean of the adjusted risk ratios  $R_{i_0 i_1} = \exp(\bar{d}(i_0, i_1)) = \exp(\sum d_j(i_0, i_1)/7)$

5. Conduct a two-way ANOVA on the log ratio-residuals, using triplet and arm, which is the three-arm extension of a paired t-test: The residual MSE, which has 12 degrees of freedom, is used to compute the empirical standard error of the log intervention effect (mean pairwise difference in log ratio-residuals)

$$s_d = \sqrt{\frac{2 \times \text{MSE}}{7}}$$

6. Carry out paired t-test on differences in mean log adjusted risk ratio,

$$t(i_0, i_1) = \frac{\bar{d}(i_0, i_1)}{s_d}$$

The computed value of  $t(i_0, i_1)$  is compared to a  $t$  distribution statistic with 12 degrees of freedom.

7. The confidence interval for the mean log adjusted risk ratio is computed as:

$$\bar{d}(i_0, i_1) \pm t_{12, 0.025} \times s_d$$

This will be back transformed and reported as an adjusted risk ratio.

#### 1.4.1.1 Subgroup analyses

The analysis of proportion virally suppressed in the community will be conducted for the following subgroups (for each subgroup, two-stage analysis would no longer be adjusted for that subgroup):

- Men and women
- Younger and older (<25, ≥25 yo)
- Younger men, Older men, Younger women, Older women
- Amongst persons who do/do not self-report HIV+, and those who SR HIV+ and current ART use at PC24.

#### 1.4.2 ***Viral suppression and Resistance***

**Question:** Does the PopART intervention affect the probability of viral suppression amongst people who self-report being currently on ART or ever being on ART?

Endpoint: Viral load suppressed (<400 copies/mL)

Cohort: Community viral load subset PC24: The subset of visits from the PC24 community viral load cohort, restricted to specimens collected from participants who self-report current ART at 24 months. A second analysis will examine viral load suppression in participants who ever report ART use up through PC24.

**Analysis:** The analysis approach will be the same as used for the two-stage analysis of proportions (see Community Viral Load objective)

**Question: Does the PopART intervention affect the probability of ART resistance at 24 months amongst people who initiate ART after the commencement of PopART, among those not virally suppressed at 24 months?**

Endpoint: Resistance to drugs used in current first or second line ARV treatment regimens

Cohort: Subset of community viral load assessed at PC24, restricted to those with VL > 400:

Details: A subset of visits from the PC24 community viral load cohort where VL exceeds 400 copies/ml will be assessed for ARV resistance, restricted to participants who self-report any initiation of ART up through PC24 after commencement of PopART.

**Analysis:** The analysis approach will use the two-stage approach for proportions.

**Question: Does the PopART intervention affect the probability of ART resistance amongst PC seroconverters?**

Endpoint: Resistance to drugs used in current first and second line ARV treatment regimens

Cohort: Seroconverter cohort

**Analysis:** The analysis approach will use the two-stage approach for proportions.

#### ***1.4.3 Viral Burden in the community***

**Question: Does the PopART intervention decrease the viral burden in the community?**

It has been established that persons with undetectable viral load are not infectious, thus HIV incidence is likely predicted by the proportion of the community with detectable viral load.

Endpoint: Viral burden is defined as

= 0 if HIV-uninfected, or if HIV-infected with VL < 400 copies/ml

= 1 If HIV-infected with unsuppressed viral load ( $\geq 400$  copies/mL)

Cohort: PC24

**Analysis:** The analysis approach will be the same as used for the two-stage analysis of proportions (see Community Viral Load objective)

Details: All persons with HIV status evaluated at PC24 visit are included.

#### ***1.4.4 HSV2 Incidence***

**Question: Does the PopART intervention change HSV-2 incidence?**

Cohort: PC, restricted to the subset of participants who are not infected with HSV-2 at PC0.

Endpoint: HSV-2 status at PC36

**Analysis:** As HSV-2 acquisition is only assessed once, at PC36, HSV2 acquisition will be assessed as a binary outcome, rather than as a survival analysis outcome. The analysis approach will use the two-stage analysis for proportions (see the analysis of community viral load). HSV-2 acquisition is considered to be both a marker of sexual activity and a risk factor for HIV acquisition.

Individual covariates included in adjustment:

- a. Age in groups (18-24, 25-29, 30-34, 35-39, 40+)
- b. Sex
- c. Interaction of Sex and Age

### 1.4.5 HIV Testing

**Question:** How much did PopART increase recent knowledge of HIV-Status (within the past year) through HIV testing and retesting in each arm, in each year of the study.

**Cohort:** PC

**Endpoint:** Self-reported knowledge of HIV status by recent testing.

**Details:** All enrolled participants with study assessed HIV status will be included. Analysis will also evaluate knowledge separately for HIV infected (see below).

Self-report of HIV status and recent testing is recorded in PC0, PC12, PC24 and PC36. A known a priori caveat for this analysis is that all participants in the PC are offered rapid HIV testing by the research enumerators at each PC visit, thus uptake of testing may be higher in the PC participants than the general population, particularly in Arm C.

PopART is expected to increase the proportion of persons with recent, accurate knowledge of HIV status. Accurate knowledge of HIV status has four mutually exclusive categories, described below. The binary endpoint for assessing the PopART effect is Known vs Unknown

Among HIV-infected:

- Known; Self-reported HIV-infected
- Unknown (refused to answer; has never been tested; did not self-report HIV-infected)

Among HIV uninfected

- Known; Self-reported HIV uninfected, testing in past year
- Unknown; No testing in past year, refused to answer; has never been tested.

**Descriptive:** Number and proportion for knowledge of HIV status will be reported over time in each community and for each arm (participant-aggregated), with 95% confidence limits based on the binomial distribution, adjusted for within community correlation.

**Analysis:** Estimates of the relative decrease (i.e. risk ratio) within a pair of study arms will use the two-stage analysis method described for proportions (see Community Viral Load) for each study round.

1. Logistic regression will be used to adjust for confounding variables at the individual level. The regression model will include terms for the covariates of interest and triplet but not trial arm.

$$\text{logit}(y_{ijk_m}) = \alpha_j + \sum_{l,m} \gamma_l z_{ijk_m l}$$

where  $y_{ijk}$  is the binary indicator of self-reported HIV-positive status for the  $k^{\text{th}}$  ( $k = 1 \dots N_{ij}$ ) individual's  $m^{\text{th}}$  year,  $i$  is  $i^{\text{th}}$  study arm ( $i = 1, 2, 3$ ),  $j$  is  $j^{\text{th}}$  study triplet ( $j = 1 \dots 7$ ), and  $z_{ijk_m l}$  is the covariate value for the  $l^{\text{th}}$  covariate.

Individual level covariates to be used for adjustment are:

- a) Age at visit in groups (18-24, 25-29, 30-34, 35-39, 40+)
- b) Sex
- c) Age x Sex interaction

**Note:** No adjustment is currently planned for community level covariates. If adjustment for a community level covariate is included, the degrees of freedom in the paired t-test will be reduced by 1.

2. A fitted model will be used to obtain the ratio of observed (O) to expected (P) proportions, and a log transformation will be applied to this ratio-residual. The expected proportion in the  $j^{\text{th}}$  triplet of the  $i^{\text{th}}$  study arm in the  $m^{\text{th}}$  year is calculated as:

$$p_{ij}^m = \sum_k \hat{y}_{ijk_m} = \sum_k \frac{\exp(\hat{\alpha}_j + \sum_l \hat{\gamma}_l z_{ijk_{ml}})}{1 + \exp(\hat{\alpha}_j + \sum_l \hat{\gamma}_l z_{ijk_{ml}})}$$

3. The ratio-residual for the  $j^{\text{th}}$  triplet of the  $i^{\text{th}}$  study arm in the  $m^{\text{th}}$  year is calculated as:

$$R_{ij}^m = \frac{o_{ij}^m}{p_{ij}^m}$$

where  $o_{ij}^m$  is the observed proportion of events in the  $i^{\text{th}}$  arm of the  $j^{\text{th}}$  triplet in the  $m^{\text{th}}$  year. The adjusted risk ratio for each triplet for arms  $i_0$  and  $i_1$  (omitting the year subscript) is calculated as:

$$\rho_j(i_0, i_1) = \frac{R_{i_0j}}{R_{i_1j}}$$

Stage 2:

4. Take the logarithm of the adjusted risk ratios:

$$d_j(i_0, i_1) = \log(\rho_j(i_0, i_1))$$

The point estimate of the intervention risk ratio comparing arms  $i_0$  and  $i_1$  is the geometric mean of the adjusted risk ratios  $R_{i_0i_1} = \exp(\bar{d}(i_0, i_1)) = \exp(\sum d_j(i_0, i_1)/7)$

5. Conduct a two-way ANOVA on the log ratio-residuals using triplet and arm, which is the three-arm extension of a paired t-test: The residual MSE, which has 12 degrees of freedom, is used to compute the empirical standard error of the log intervention risk ratio (mean pairwise difference in log ratio residuals between arms)

$$s_d = \sqrt{\frac{2 \times \text{MSE}}{7}}$$

6. Carry out paired t-test on log adjusted risk ratio ,

$$t(i_0, i_1) = \frac{\bar{d}(i_0, i_1)}{s_d}$$

The computed value of  $t(i_0, i_1)$  is compared to a  $t$  distribution statistic with 12 degrees of freedom.

7. The confidence interval for the log adjusted risk ratio is computed as:

$$\bar{d}(i_0, i_1) \pm t_{12, 0.025} \times s_d$$

This will be back transformed and reported as an adjusted risk ratio.

**Question: How much did PopART increase accurate knowledge of HIV-infected status through HIV testing and retesting in each arm, in each year of the study? (First 90)**

**Cohort:** PC. For each year, all participants assessed with HIV-infected status by study testing that year are included

Endpoint: Accurate knowledge of HIV-infected status.

Details: All enrolled participants who are assessed as HIV-infected are included.

Knowledge of true HIV-infected status has 3 mutually exclusive categories

- Self-reported HIV-infected
- Tested in last year, did not SR HIV+
- Did not test in last year, did not SR HIV+

The binary endpoint for assessing the PopART intervention is Accurate knowledge of HIV-infected status, i.e. HIV+ who SR-HIV+ and Not SR-HIV+ (remaining categories). PopART is expected to increase the proportion of persons with “Accurate knowledge of HIV-infected status”.

Descriptive: Number and proportions in each of the 3 categories and classified as Accurately known will be reported for each year in each community and for each arm (participant-aggregated), with 95% confidence limits based on the binomial distribution, adjusted for within community correlation.

Analysis: Estimates of the relative increase within a pair of study arms will use the two-stage analysis method described for proportions (see Community Viral Load) for each study round separately.

#### ***1.4.6 Retention in care***

**Question: Does the PopART intervention increase retention in HIV care in each community?**

Cohort: Self-reported HIV-infected cohort, restricted to participants who report having never registered for care

Endpoint: HIV care visit within the past three months

PopART is expected to increase the proportion of persons retained in care (i.e. with HIV care visit within the past 3 months).

Descriptive: Number and proportion will be reported for each year in each community and for each arm (participant-aggregated), with 95% confidence limits based on the binomial distribution, adjusted for within community correlation.

Analysis: Estimates of the relative increase within a pair of study arms will use the two-stage analysis method described for proportions for each study round separately.

#### ***1.4.7 Viral Load Suppression***

**Question: Does the PopART intervention increase viral load suppression in each community at PC12 and PC36?**

Cohort: PC12 and PC36 community viral load

Endpoint: Plasma Viral Load

Details: Viral load is assessed in a random sample of 75 HIV-infected participants in each of PC0, PC12, and PC36. See also Interim Analysis for PC12.

Descriptive: Number and proportion virally suppressed will be presented in each community and each year. The characteristics of (log) viral load in each community will be presented: mean, median, SE, range.

Analysis: A paired t-test on the unadjusted pairwise rate ratios for each year will be used to test for change in proportion virally suppressed in each pair of arms across triplets for PC12 and PC36 separately.

#### ***1.4.8 ART screening and uptake (Second 90)***

**Question: What are the proportions of HIV-infected [with known status] on ART in each arm, in each year of the study?**

**Question: How much does PopART increase ARV treatment?**

Cohorts:

- 1) HIV-infected Cohort (PC0, PC12, PC24, PC36)
- 2) Self-reported HIV infected cohort

Endpoint: Self-reported ART

PopART is expected to increase the proportion reporting ART amongst HIV infected.

Details: ART is only assessed in participants who self-report HIV-infected status and can be self-reported and/or verified by ART documents presented by the participant. We will examine the increase in treatment amongst 1) HIV-infected participants identified in study testing and 2) participants who self-identify as HIV-infected. The same analysis approach will be used as for retained in care.

Descriptive: Proportions will be tabulated for all communities each year for each arm (participant-aggregated), for each analysis with 95% confidence limits based on the binomial distribution.

Estimates of the relative increase within a pair of study arms each year will use the analysis method described for proportions (see Community Viral Load).

#### ***1.4.9 HIV diagnosis and initiation of care***

**Question: For person newly diagnosed with HIV in the prior year, what proportion are linked to care within 6 months in each arm, in each year of the study?**

Cohort: Combined subsets of PC0, PC12, PC24, PC36, restricted to persons who self-report first diagnosis of HIV-infection in the prior year.

Endpoint: Registered for HIV Care within 6 months

Details: Registering for HIV care is only assessed in those who self-report HIV-infected status and can be self-reported and/or verified by documents presented by the participant. Registering for care will be assessed using both the PC visit where diagnosis is reported and the subsequent PC visit. We will examine registered for HIV Care and time to registration amongst participants who self-identify as HIV-infected.

Description: Proportions registered within 6 months will be tabulated for all communities each year.

Analysis: Estimates of the relative increase within a pair of study arms in each Follow-up round will use the analysis method described for proportions (see Community Viral Load) in the follow-up years.

#### ***1.4.10 Sexual risk behavior***

**Question: Does the PopART intervention change sexual behaviors?**

The PopART intervention does not directly target change in sexual behavior, although an increase in knowledge of HIV may result in change in sexual risk, for example as a result of risk disinhibition due to availability of treatment, effects due to behavioral counseling by CHiPs and condom promotion, and increased knowledge of HIV status throughout the community (including in discordant partners).

Endpoints: The following sexual behaviors will be examined separately for men and women:

- More than one sexual partner in the prior year



- Any casual/one-time sex partners in the last year
- Unprotected sex the last time.
- In the extended sexual behavior questionnaire:
  - Any concurrent sexual partners
  - Inconsistent or no condom use with any partners
  - Any sex for money/or gifts
  - Any known HIV discordant relationships

Cohort:

- 1) PC, by gender
- 2) Risk subgroups of the PC, by gender

Details: Detailed partner by partner questions about sexual risk behavior are only asked in the 20% Risk subgroup of the PC. Analyses of sexual behavior will all be sex specific.

Descriptive: Proportions reporting each sexual behavior will be tabulated for all communities and by arm (participant aggregated) each year.

Analysis. Estimates of the relative increase within a pair of study arms each year will use the analysis method described for proportions (see Community Viral Load) in the follow-up years.

Subgroups:

- By HIV status at visit as determined by study testing
- By self-reported HIV status at visit
- Age group

#### ***1.4.11 HIV disease progression and death***

Disease progression not assessed in PC. A detailed plan to analyze a limited set of clinical data assessing HIV disease progression and death for PC participants who consented to clinical data access will be developed at a later date in a separate document.

#### ***1.4.12 ART toxicity based on clinic records***

ART toxicity not currently assessed in PC. We continue to work to obtain data from clinics to assess ART toxicity.

#### ***1.4.13 Case notification rate of tuberculosis***

Case notification of tuberculosis not currently assessed in PC. We continue to work to obtain data from clinics to assess TB case notifications, however the primary assessment of changes in TB case notification will be measured using clinic notification data, and based on linkage of PC data to clinic data for individuals who self-report they have taken treatment for TB in the previous 12 months (with linked clinic data being used to determine if an individual had bacteriologically confirmed TB).

#### ***1.4.14 HIV-related stigma***

**Question: Does PopART change HIV Stigma?**

Cohort:

- 1) PC stigma subset

## 2) Self-Reported HIV-infected cohort

Endpoint:

- 1) HIV-related Stigma Scores
- 2) HIV-infected Stigma Scores

Details: HIV Stigma is assessed on a randomly selected 20% sample of the PC participants in PC0, PC12, PC24 and PC36 using 12 questions measured using a 4-point Likert scale. Experience of HIV stigma using a different set of 12 questions measured on a Likert Scale is measured in all self-identified HIV-positive participants.

Analysis: Mean stigma scores and binary indicators of stigma, developed by the Stigma Working Group, will be reported for each community and each year. Estimates of the relative change within a pair of study arms each year will use the two-stage analysis method for comparing adjusted community means and prevalences within each triplet described below

Subgroups. HIV Stigma effects will be assessed in the following subgroups

- Sex
- Country
- Age

**Analysis:** Estimates of the mean change within a pair of study arms will use the two-stage analysis method described for means for each study round.

Stage 1.

1. Linear regression will be used to adjust for confounding variables at the individual level. The regression model will include terms for the covariates of interest and triplet but not trial arm.

$$y_{ijk_m} = \alpha_j + \sum_{l,m} \gamma_l z_{ijk_{ml}}$$

where  $y_{ijk}$  is the stigma score for the  $k^{th}$  ( $k = 1 \dots N_{ij}$ ) individual's  $m^{th}$  year,  $i$  is  $i^{th}$  study arm ( $i = 1,2,3$ ),  $j$  is  $j^{th}$  study triplet ( $j = 1 \dots 7$ ), and  $z_{ijk_{ml}}$  is the covariate value for the  $l^{th}$  covariate.

Individual level covariates to be used for adjustment are:

- a) Age at visit in groups (18-24, 25-29, 30-34, 35-39, 40+)
- b) Sex
- c) Age x Sex interaction

Note: No adjustment is currently planned for community level covariates. If adjustment for a community level covariate is included, the degrees of freedom in the paired t-test will be reduced by 1.

2. A fitted model will be used to obtain the difference of observed (O) to expected (P) means. The expected mean in the  $j^{th}$  triplet of the  $i^{th}$  study arm in the  $m^{th}$  year is calculated as:

$$p_{ij}^m = \sum_k \hat{y}_{ijk_m} = \sum_k \hat{\alpha}_j + \sum_l \hat{\gamma}_l z_{ijk_{ml}}$$

3. The difference residual for the  $j^{th}$  triplet of the  $i^{th}$  study arm in the  $m^{th}$  year is calculated as:

$$R_{ij}^m = o_{ij}^m - p_{ij}^m$$

where  $o_{ij}^m$  is the observed means in the  $i^{th}$  arm of the  $j^{th}$  triplet in the  $m^{th}$  year.

Stage 2:

4. The point estimate of the intervention effect is the mean adjusted difference for each triplet for arms  $i_0$  and  $i_1$  (omitting the year subscript), calculated as:

$$\bar{d}_j(i_0, i_1) = R_{i_0j}^m - R_{i_1j}^m$$

5. Conduct a two-way ANOVA on the difference residuals, using triplet and arm, which is the three-arm extension of a paired t-test: The residual MSE, which has 12 degrees of freedom, is used to compute the empirical standard error of the intervention effect (mean pairwise difference in different residuals between arms)

$$s_d = \sqrt{\frac{2 \times \text{MSE}}{7}}$$

6. Carry out paired t-test on mean pairwise differences,

$$t(i_0, i_1) = \frac{\bar{d}(i_0, i_1)}{s_d}$$

The computed value of  $t(i_0, i_1)$  is compared to a  $t$  distribution statistic with 12 degrees of freedom.

7. The confidence interval for the mean adjusted difference is computed as:

$$\bar{d}(i_0, i_1) \pm t_{12, 0.025} \times s_d$$

#### ***1.4.15 Medical male circumcision (MMC)***

**Question: What proportion of uncircumcised [self-reported] HIV-uninfected men received MMC during the PopART intervention by arm overall and by year?**

**Question: How much did the PopART intervention increase MMC among [self-reported] HIV-uninfected men?**

Cohort

- 1) Self-reported HIV-uninfected men: The PC, restricted to men in the PC who self-report not having had MMC at enrollment and did not self-report HIV-infected status.
- 2) HIV-uninfected men cohort: All men in the PC who self-report not having had MMC at enrollment and were HIV-uninfected by study testing.

Endpoint: Overall: Proportion of the cohort with MMC occurring after the initiation of the PopART intervention. Each year: the proportion reporting MMC within the previous year, assessed each year.

Analysis: Proportion of new MMC will be reported for each community for each year.

PopART is expected to increase the proportion of HIV uninfected men who receive MMC. Estimates of the relative change in MMC in within a pair of study arms each year will use the two-stage method for comparing community proportions, i.e., a  $t$ -test for the within triplet adjusted proportions.

It is known that the baseline prevalence of traditional male circumcision is much higher in South Africa than Zambia: If the baseline prevalence of male circumcision is not well balanced in each triplet, this may be used as a community level covariate.

Subgroups:

- Country
- Age

## **I.5 Intervention Delivery Objectives: CHiPs data**

The CHiPs data will be used to measure participation of households and individuals in the CHiP intervention, and uptake of key components of the intervention. Data are available for all 7 Arm A and all 7 Arm B communities, but not for Arm C.

We have aligned how uptake of the intervention will be measured using CHiPs data, with how it will be measured using Population Cohort data, as far as possible. However, a fundamental difference between the PC and the CHiPs intervention, is that in the PC all participants consent to give a blood sample for laboratory HIV testing, so that HIV status is known for close to 100% of PC participants. In contrast, in the CHiPs intervention individuals can choose to participate but choose not to accept HIV testing using a rapid HIV test. This means that, among individuals who consent to participate in the CHiPs intervention, HIV status is known for individuals who self-report they are HIV-infected, or accept the offer of rapid HIV testing, or report they have recently tested for HIV and the test result was HIV-negative (for example in the previous 12 months); and HIV status is unknown for all other individuals.

All of the main outcomes will be summarised as proportions. Two examples are:

- (1) the proportion of individuals who know their HIV status, among all individuals who consent to participate in the intervention [see I.4.4 for measurement in the PC]
- (2) the proportion of HIV-infected individuals who link to HIV care within 6 months of referral to HIV care, among all who were referred to HIV care by CHiP teams and were not on ART at the time of referral, derived from a “time to event” analysis [see I.4.8 for measurement in the PC].

The general approach to data analysis will be to summarise data:

1. separately for each community
2. average value across the 14 intervention communities
3. average values for each country
4. average values for each trial arm
5. average values for each trial arm, within each country

Average values will be calculated as the average of the percentage values from each of the communities, as well as average values based on individual-level data (giving each individual the same weight in the analysis, rather than giving each community the same weight).

For almost all intervention components, uptake is expected to be similar in Arms A and B. The exception is ART uptake, because of the difference between the two trial arms for ART eligibility criteria up to the date when all Arm B communities transition to offering universal treatment. Thus in summarizing uptake of the intervention, the emphasis will be on summaries 1, 2, 3, 4 and 5 above. For ART uptake, time to start ART after referral to HIV care, and retention on ART the emphasis will be on summaries 1, 4, and 5.

There will be 3 rounds (“years”) of delivering the CHiPs intervention. Uptake of all intervention components will be summarized separately for each round.

As well as overall summaries, subgroup analysis will also be presented by gender, age group, by age group for each gender, and according to participation and residency in earlier rounds of the

intervention. Sub-group analyses beyond those by age group, gender, and prior participation and residency, are specified separately if applicable.

The analysis for six outcomes that are measured directly using the CHIP data is set out below in detail, chosen on the basis that they are among the most important intervention components. The six outcomes are knowledge of HIV status, the time to link to HIV care after referral to HIV care, ART uptake, retention in HIV care, retention on ART, and uptake of MMC. Various other outcomes will also be measured, including for example the proportion of households that participate in the intervention, the proportion of individuals that participate in the intervention, the uptake of re-testing for HIV after a previous HIV-negative test result, and the time to start ART after referral to HIV care in Arm A communities. In addition, we set out our approach to estimating coverage against the UNAIDS “90-90” targets that 90% of HIV-positive individuals know their HIV-positive status, and that 90% are on ART among those who know their HIV-positive status.

As well as the descriptive summaries outlined above, we will formally compare key outcomes between Arm A and Arm B, using the same 2-stage method of analysis as has been outlined above for the analysis of PC data. In the case of the intervention data, all outcomes are measured as a binary outcome (yes/no) i.e. as a proportion.

### ***1.5.1 Knowledge of HIV status***

**Question: How much did PopART increase recent knowledge of HIV-Status (within the past year) through HIV testing and retesting, in each round (“year”) of the study.**

PopART is expected to achieve high levels of knowledge of HIV status.

Cohort: All who are contacted by CHIP teams and consent to participate in the intervention, separately for each round (“year”) of the study.

Endpoint: Knowledge of HIV status, self-reported or from accepting the offer of rapid HIV testing from CHIP teams.

Details: All individuals who are contacted by CHIP teams and consent to participate in the intervention are included. Knowledge of HIV status has five mutually exclusive categories. The binary endpoint for assessing the PopART effect is Known vs Unknown

- Known; Self-reported HIV-infected
- Known; Accepted offer of rapid HIV testing from CHIP teams
- Known; Self-reported HIV uninfected, reports recently tested for HIV elsewhere [“recently” tested will be defined in at least 2 ways: testing in past 3 months, and testing in past year (12 months)]
- Unknown (previously tested but did not disclose result of most recent HIV test; has never been tested)
- Unknown; Self-reported HIV uninfected, no testing in past year

**Analysis:** Number and proportion who know their HIV status will be reported in each community, for each country, for each arm, and overall, with 95% confidence limits based on the binomial distribution when summarizing proportions separately for each community. For the other analyses, which report average values across communities, the clustering in the data will be accounted for by calculating standard errors and corresponding confidence intervals based on the between-community variation in the proportion with the outcome (beyond that explained by country and trial arm).

## Subgroups

- Pregnant women

### ***1.5.2 HIV diagnosis and initiation of care***

**Question:** For individuals who are identified as HIV-infected by the CHIP teams, either through self-report of HIV-infected status or from accepting a rapid HIV test from the CHIP teams and the test result was HIV-positive, what proportion are linked to care within 6 months in each round (“year”) of the study?

PopART is expected to result in faster linkage to HIV care after HIV diagnosis and/or referral to HIV care.

Cohort: All individuals who were contacted, consented to participate, were identified as HIV-infected and not on ART, and were referred to HIV care by the CHIP teams, separately for each round (“year”) of the study.

Endpoint: Registered for HIV Care within 6 months of referral to HIV care.

Details: Registering for HIV care is only assessed in those who are identified by the CHIP teams as HIV-positive and can be self-reported and/or verified by documents presented by the individual.

**Analysis:** Number and proportion who have registered for HIV care within 6 months of referral to HIV care, among all individuals who were identified as HIV-infected and were referred to HIV care and were not taking ART at the time of referral, derived from a “time-to-event” analysis. Proportions will be reported for each community, for each country, for each arm, and overall, with 95% confidence limits based on the “time-to-event” (Kaplan-Meier) analysis when summarizing proportions separately for each community. For the other analyses, which report average values across communities, the clustering in the data will be accounted for by calculating standard errors and corresponding confidence intervals based on the between-community variation in the proportion with the outcome (beyond that explained by country and trial arm).

## Subgroups

- Pregnant women
- Newly diagnosed HIV-positive; self-reported HIV-positive and never previously registered for HIV care

### ***1.5.3 ART uptake among HIV-infected individuals***

**Question:** What are the proportions of HIV-infected individuals who are on ART in each arm, among individuals who have been identified as HIV-infected by the CHIP teams, in each round (“year”) of the study?

**Question:** How much did PopART increase ART uptake?

PopART is expected to increase the proportion reporting ART amongst HIV infected individuals, especially in Arm A.

Cohort: All individuals who are contacted by CHIP teams, consent to participate in the intervention, and are identified by CHIP teams as HIV-infected either because they self-report they are HIV-infected or because they accept the offer of rapid HIV testing from the CHIP teams and the test result is HIV-positive, separately for each round (“year”) of the study.

Endpoint 1: Self-reported ART at time of the annual household visit.

**Endpoint 2:** Self-reported ART at the end of the round (“year”), using the most recently available information from follow-up visits made to individuals who have been identified as HIV-infected, with the denominator restricted to individuals who were still resident in the same area of the community at the end of the round according to the last information collected through CHIP follow-up visits during the round.

Details: ART is only assessed in individuals who are identified by the CHIP teams as HIV-positive and can be self-reported and/or verified by ART documents presented by the individual.

**Analysis:** Number and proportion who are taking ART, among all individuals identified as HIV-infected, will be reported in each community, for each arm, and for each arm within each country, with 95% confidence limits based on the binomial distribution when summarizing proportions separately for each community. For the other analyses, which report average values across communities, the clustering in the data will be accounted for by calculating standard errors and corresponding confidence intervals based on the between-community variation in the proportion with the outcome (beyond that explained by country and trial arm).

#### **Subgroups**

- Pregnant women

#### ***1.5.4 Retention in HIV care among HIV-infected individuals who are registered for HIV care***

**Question:** Does the PopART intervention achieve high levels of retention in HIV care, in each round (“year”) of the study?

PopART is expected to achieve high levels of retention in HIV care among HIV-infected individuals who have ever registered for HIV care.

**Cohort:** All individuals who are contacted by CHIP teams, consent to participate in the intervention, and are identified by CHIP teams as HIV-infected either because they self-report they are HIV-infected or because they accept the offer of rapid HIV testing from the CHIP teams and the test result is HIV-positive, restricted to those who as part of the annual household visit report they have previously registered for HIV care, separately for each round (“year”) of the study.

**Endpoint:** HIV care visit within the 3 months prior to the annual household visit.

**Analysis:** Number and proportion who are retained in HIV care, among all individuals identified as HIV-infected who have ever registered for HIV care, will be reported in each community, for each country, for each arm, and overall, with 95% confidence limits based on the binomial distribution when summarizing proportions separately for each community. For the other analyses, which report average values across communities, the clustering in the data will be accounted for by calculating standard errors and corresponding confidence intervals based on the between-community variation in the proportion with the outcome (beyond that explained by country and trial arm).

#### **Subgroups**

- First registered for HIV care before or after PopART study started (pre- or post-2014)

#### ***1.5.5 Retention on ART among HIV-infected individuals who have ever taken ART***

**Question:** Does the PopART intervention achieve high levels of retention on ART, in each round (“year”) of the study?

PopART is expected to achieve high levels of retention on ART among HIV-infected individuals who have ever taken ART.

**Cohort:** All individuals who are contacted by CHiP teams, consent to participate in the intervention, and are identified by CHiP teams as HIV-infected either because they self-report they are HIV-infected or because they accept the offer of rapid HIV testing from the CHiP teams and the test result is HIV-positive, restricted to those who have reported at least once that they have “ever” taken ART, separately for each round (“year”) of the study. For example, for round 2 (“year 2”) of the study, HIV-infected individuals are included in the analysis if they have reported, at one or more of the Round 1 and Round 2 annual household visits or a follow-up visit made at any time up to the Round 2 annual household visit, that they have “ever” taken ART.

**Endpoint:** Taken ART within the 1 month prior to the annual household visit and missed no pills in the previous 3 days.

**Analysis:** Number and proportion who are retained on ART, among all individuals identified as HIV-infected who have ever taken ART at the time of the annual household visit, will be reported in each community, for each arm, and for each arm within each country, with 95% confidence limits based on the binomial distribution when summarizing proportions separately for each community. For the other analyses, which report average values across communities, the clustering in the data will be accounted for by calculating standard errors and corresponding confidence intervals based on the between-community variation in the proportion with the outcome (beyond that explained by country and trial arm).

### **Subgroups**

- First started ART before or after PopART study started (pre- or post-2014)

### ***1.5.6 Uptake of MMC among HIV-uninfected men***

**Question: What proportion of uncircumcised [self-reported] HIV-uninfected men were circumcised during the PopART intervention, in each round (“year”) of the study?**

**Cohort 1:** Men who are contacted by CHiP teams and consent to participate in the intervention, report they are not circumcised or do not know their circumcision status, and accept the offer of HIV testing from CHiP teams and the test result is HIV-negative, and are still resident in the community one year later, separately for each round (“year”) of the study.

**Endpoint 1:** MMC within the previous year (self-reported), among men who in the previous round (“year”) reported they were not circumcised and tested HIV-negative. This endpoint can be measured from Round 2 onwards.

**Cohort 2:** Men who are contacted by CHiP teams and consent to participate in the intervention, and accept the offer of HIV testing from CHiP teams and the test result is HIV-negative, separately for each round (“year”) of the study

**Endpoint 2:** MMC, at any time prior to the annual household visit

**Cohort 3:** Men who are contacted by CHiP teams and consent to participate in the intervention and accept the offer of HIV testing from CHiP teams and the test result is HIV-negative, and report they are not circumcised or do not know their circumcision status, separately for Rounds (“years”) 2 and 3 of the study.



Endpoint 3: MMC (self-reported), among men who accepted a referral for MMC [in Rounds 2 and 3, the protocol was for CHiPs to conduct one follow-up visit to men they had referred for MMC, >1 month after the referral date].

PopART is expected to increase the proportion of HIV-uninfected men who are circumcised with MMC. Endpoint 2 measures the uptake of MMC among all HIV-uninfected men, regardless of when MMC was done, and so provides a cumulative measure of MMC uptake.

**Analysis:** Number and proportion of HIV-uninfected men who are circumcised with MMC will be reported in each community, for each country, for each arm, and overall, with 95% confidence limits based on the binomial distribution when summarizing proportions separately for each community. For the other analyses, which report average values across communities, the clustering in the data will be accounted for by calculating standard errors and corresponding confidence intervals based on the between-community variation in the proportion with the outcome (beyond that explained by country and trial arm).

### ***1.5.7 Estimates of coverage against the first two of the UNAIDS 90-90-90 targets***

**Question:** How much did PopART increase coverage against the first 90 target (90% of HIV-positive individuals know their HIV-positive status) and the second 90 target (among HIV-positive individuals who know their HIV-positive status, 90% are on ART), in each round (“year”) of the study.

PopART is expected to achieve high levels of coverage against the 90-90 targets.

#### **1.5.7.1 Estimates of coverage against the first 90 target**

**Cohort 1:** All who are contacted by CHiP teams and consent to participate in the intervention, and are HIV-positive, separately for each round (“year”) of the study. The number of HIV-positive individuals among all who participated in the round is calculated as the sum of: (1) the number who were known by the CHiPs to be HIV-positive, because they self-reported they were HIV-positive to the CHiPs or they were newly diagnosed HIV-positive by the CHiPs based on a rapid HIV test; and (2) an *estimated* number among those whose HIV status was not known to CHiPs. For (2), our “central” estimate is that HIV prevalence among individuals whose HIV status is not known to the CHiPs is the same as among those who accepted the offer of HIV testing, stratified on all combinations of community, gender, age group, and participation and residency in the previous round. For (2), sensitivity analysis is done assuming that HIV prevalence among individuals whose HIV status is not known to the CHiPs is 2-3 times higher than among those who accepted the offer of HIV testing.

#### **Endpoint 1a: “Central estimate”**

(i) At start of the round: Knowledge of HIV-positive status is defined as self-reported HIV-positive (this implicitly assumes that among the HIV-positive individuals whose HIV-positive status is not known to the CHiPs, none know their HIV-positive status).

(ii) By the end of the round: Knowledge of HIV-positive status is defined as self-reported HIV-positive or newly diagnosed HIV-positive by the CHiPs (this implicitly assumes that among the HIV-positive individuals whose HIV-positive status is not known to the CHiPs, none know their HIV-positive status).

#### **Endpoint 1b: “Sensitivity analysis estimate”**

(i) At start of the round: Knowledge of HIV-positive status is defined as self-reported HIV-positive, plus a *proportion* of those who are HIV-positive, but their HIV-positive status is not known to the CHiPs. Among those who are HIV-positive but their HIV-positive status is not known to CHiPs, three alternative assumptions are made for the percentage who know their HIV-positive status (i) the percentage who know their HIV-positive status is the *same* as the “at start of round” value for adults whose HIV status is

known to CHiPs i.e. equal to (self-reported HIV-positive to CHiPs / total known by the CHiPs to be HIV-positive by the end of the round) (ii) the percentage who know their HIV-positive status is *half* of the “at start of round” value among adults whose HIV-positive status is known to CHiPs by the end of the round (iii) the percentage who know their HIV-positive status is 0%.

(ii) By the end of the round: - Knowledge of HIV-positive status is defined as self-reported HIV-positive or newly diagnosed HIV-positive by the CHiPs, plus a *proportion* of those who are HIV-positive, but their HIV-positive status is not known to the CHiPs. Among those who are HIV-positive but their HIV-positive status is not known to CHiPs, three alternative assumptions are made for the percentage who know their HIV-positive status (i) the percentage who know their HIV-positive status is the *same* as the “at start of round” value for adults whose HIV status is known to CHiPs i.e. equal to (self-reported HIV-positive to CHiPs / total known by the CHiPs to be HIV-positive by the end of the round) (ii) the percentage who know their HIV-positive status is *half* of the “at start of round” value among adults whose HIV-positive status is known to CHiPs by the end of the round (iii) the percentage who know their HIV-positive status is 0%.

**Details:** All individuals who are contacted by CHiP teams and consent to participate in the intervention and are HIV-positive are included.

**Cohort 2:** All who are a household member in the community during the round - i.e. both individuals who are contacted and consent to participate in the intervention (equal to Cohort 1) and also those who are not contacted by CHiPs and those who are contacted but do not consent to participate in the intervention - and are HIV-positive, separately for each round (“year”) of the study. The number of HIV-positive individuals among all who participated in the round is calculated as for Cohort 1, for both “central” and “sensitivity analysis” estimates. The number of HIV-positive individuals among all who did not participate in the round is calculated with the assumption that HIV prevalence is the same among non-participants as among participants, stratified on all combinations of community, gender, age group, and participation and residency in the previous round; in sensitivity analysis HIV prevalence among non-participants is varied in the range 80%-125% of the “central” estimate.

**Endpoint 2a: “Central estimate”.**

(i) At start of the round: For individuals who participated in the round, knowledge of HIV-positive status is defined as for Endpoint 1a, i.e. as self-reported HIV-positive to CHiPs. Among all who did not participate in the round, the number of HIV-positive individuals who know their HIV-positive status is calculated with the assumption that the proportion who know their HIV-positive status is the same as among participants *at the start of the round*, stratified on all combinations of community, gender, age group, and participation and residency in the previous round.

(ii) By the end of the round: For individuals who participated in the round, knowledge of HIV-positive status is defined as for Endpoint 1a, i.e. as self-reported HIV-positive to CHiPs or newly diagnosed HIV-positive by CHiPs. Among all who did not participate in the round, the number of HIV-positive individuals who know their HIV-positive status is calculated with the assumption that the proportion who know their HIV-positive status by the end of the round is the same as among participants *at the start of the round*, stratified on all combinations of community, gender, age group, and participation and residency in the previous round – i.e. the assumption is that their knowledge of HIV-positive status does not change during the round, equivalent to assuming (conservatively) that non-participants do not receive HIV testing services during the round.

**Endpoint 2b: “Sensitivity analysis estimate”.**

(i) At start of the round: For individuals who participated in the round, knowledge of HIV-positive status is defined as for Endpoint 1b. Among all who did not participate in the round, the proportion who know their HIV-positive status is varied in the range 80%-125% of the estimated proportion among participants *at the start of the round*.

(ii) By the end of the round: For individuals who participated in the round, knowledge of HIV-positive status is defined as for Endpoint 1b. Among all who did not participate in the round, the proportion who know their HIV-positive status is varied in the range 80%-125% of the estimated proportion among participants *at the start of the round*.

**Details:** All individuals who are a household member during the round, and are HIV-positive, are included.

**Analysis:** Number and proportion who know their HIV-positive status will be reported in each community, for each country, for each arm, and overall, with uncertainty intervals based on the sensitivity analyses. For the other analyses, which report average values across communities, the clustering in the data will be accounted for by calculating standard errors and corresponding confidence intervals based on the between-community variation in the proportion with the outcome (beyond that explained by country and trial arm); this will be done both for “central” estimates and for “sensitivity analysis” estimates.

### ***1.5.8 Estimates of coverage against the second 90 target***

**Cohort 1A:** All who are contacted by CHiP teams and consent to participate in the intervention and know their HIV-positive status following the annual round visit, separately for each round (“year”) of the study. The “central estimate” of the total who know their HIV-positive status, is the total whose HIV-positive status is known to the CHiPs following the annual round visit – as described in 1.5.7.1 for Endpoint 1a. In sensitivity analysis, the total who know their HIV-positive status is varied as described in 1.5.7.1 for Endpoint 1b.

#### **Endpoint 1Aa: “Central estimate”**

(i) At start of the round: On ART (based on self-report) on the date of the annual round visit.

#### **Endpoint 1Ab: “Sensitivity analysis” estimate**

(i) At start of the round: On ART (based on self-report) on the date of the annual round visit, among those who are known by the CHiPs to be HIV-positive. Among the estimated number of individuals who know their HIV-positive status, but their HIV-positive status is not known to CHiPs, ART uptake is varied in the range 50%-100% of the value at the start of the round among those who *self-reported they were HIV-positive* to the CHiPs.

**Cohort 1B:** All who are contacted by CHiP teams and consent to participate in the intervention, and know their HIV-positive status following the annual round visit, *and are still resident in the same area of the community at the end of the round according to the last information collected from CHiP follow-up visits during the round*, separately for each round (“year”) of the study. The “central estimate” and “sensitivity analysis” estimates are calculated in the same way as for Endpoint 1Aa and Endpoint 1Ab respectively, with the additional assumption that the percentage who remain resident in the same area of the community at the end of the round among those who know their HIV-positive status but did not self-report HIV-positive to CHiPs is the *same as among those whose HIV-positive status is known to CHiPs*.

#### **Endpoint 1Ba: “Central estimate”**

(ii) By the end of the round: On ART (based on self-report) by the end of the round, according to the last follow-up information collected by CHiPs during the round.

**Endpoint 1Bb: “Sensitivity analysis” estimate**

(ii) By the end of the round: On ART (based on self-report) by the end of the round, according to the last follow-up information collected by CHiPs during the round, among those who are known by the CHiPs to be HIV-positive. Among the estimated number of individuals who know their HIV-positive status but their HIV-positive status is not known to CHiPs, ART uptake is varied in the range 50%-100% of the value *at the start of the round* among those who self-reported they were HIV-positive to the CHiPs – i.e. it is assumed that ART uptake does not increase during the round among individuals who know their HIV-positive status but their HIV-positive status is not known to CHiPs.

**Details:** All individuals who are contacted by CHiP teams and consent to participate in the intervention and are known by the CHiPs to be HIV-positive, plus an estimated number who participated in the round and know their HIV-positive status but their HIV-positive status is not known to the CHiPs following the annual round visit, are included.

**Cohort 2A:** All who were a household member in the community during the round, were HIV-positive, and knew their HIV-positive status. Thus, this cohort includes both (a) individuals who were contacted and consented to participate in the intervention (equal to Cohort 1A) and also (b) those who were not contacted by CHiPs, and those who were contacted but did not consent to participate in the intervention, separately for each round (“year”) of the study. For (b) the number who know their HIV-positive status is estimated as described in section I.5.7.1 for Endpoints 2a and 2b.

**Endpoint 2Aa: “Central estimate”**

(i) At start of the round: On ART (based on self-report) on the date of the annual round visit, among individuals who participated and are known by the CHiPs to be HIV-positive. Among individuals who did not participate in the round but know their HIV-positive status, the percentage on ART is assumed to be the same as *at the start of the round* among individuals who self-reported they were HIV-positive to the CHiPs.

**Endpoint 2Ab: “Sensitivity analysis” estimate**

(i) At start of the round: On ART (based on self-report) on the date of the annual round visit, among those who are known by the CHiPs to be HIV-positive. Among the estimated number of individuals who participated in the intervention and know their HIV-positive status, but their HIV-positive status is not known to CHiPs, the percentage on ART is varied in the range 50%-100% of the value *at the start of the round* among those who self-reported they were HIV-positive to the CHiPs. Among the estimated number who know their HIV-positive status but did not participate in the round, the percentage on ART is varied in the range 80%-125% of the estimated percentage *among participants at the start of the round [participants who either (a) self-reported they were HIV-positive to the CHiPs or (b) were estimated to know their HIV-positive status at the start of the round but did not disclose this to CHiPs]*.

**Cohort 2B:** All who were a household member in the community during the round, were HIV-positive, and knew their HIV-positive status, *and were still resident in the same area of the community at the end of the round*, separately for each round (“year”) of the study. Thus this cohort is a subset of cohort 2A; and it is assumed that, among those who know their HIV-positive status but their HIV-positive status is not known to CHiPs, the percentage who remain resident in the same area of the community at the end of the round is the same as among those whose HIV-positive status *is* known to the CHiPs.

**Endpoint 2Ba: “Central estimate”**

(ii) By the end of the round: On ART (based on self-report) by the end of the round, according to the last follow-up information collected by CHiPs during the round, among those whose HIV-positive status is known to the CHiPs. Among individuals who did not participate but know their HIV-positive status, the percentage on ART is assumed to be the same as the value *at the start of the round* among those who self-reported they were HIV-positive to the CHiPs.

**Endpoint 2Bb: “Sensitivity analysis” estimate**

(ii) By the end of the round: On ART (based on self-report) by the end of the round, according to the last follow-up information collected by CHiPs during the round, among those who are known by the CHiPs to be HIV-positive. Among the estimated number of individuals who participated and know their HIV-positive status but their HIV-positive status is not known to CHiPs, the percentage on ART is varied in the range 50%-100% of the value *at the start of the round* among those who self-reported they were HIV-positive to the CHiPs – i.e. it is assumed that ART uptake does not increase during the round among individuals who participated and know their HIV-positive status but their HIV-positive status is not known to CHiPs. Among the estimated number who know their HIV-positive status but did not participate in the round, the percentage on ART is varied in the range 80%-125% of the estimated percentage *among participants at the start of the round [participants who either (a) self-reported they were HIV-positive to the CHiPs or (b) were estimated to know their HIV-positive status at the start of the round but did not disclose this to CHiPs]*.

**Details:** All individuals who are a household member during the round, and are HIV-positive, and know their HIV-positive status, are included.

**Analysis:** Number and proportion who are on ART will be reported in each community, for each country, for each arm, and overall, with uncertainty intervals based on the sensitivity analyses. For the other analyses, which report average values across communities, the clustering in the data will be accounted for by calculating standard errors and corresponding confidence intervals based on the between-community variation in the proportion with the outcome (beyond that explained by country and trial arm); this will be done both for “central” estimates and for “sensitivity analysis” estimates.