HIV Prevention Trials Network

CLARIFICATION MEMO #01 TO:

HPTN 071

DAIDS Document ID #11865

POPULATION EFFECTS OF ANTIRETROVIRAL THERAPY TO REDUCE HIV TRANSMISSION (POPART): A CLUSTER-RANDOMIZED TRIAL OF THE IMPACT OF A COMBINATIO PREVETION PACKAGE ON POPULATION-LEVEL HIV INCIDENCE IN ZAMBIA AND SOUTH AFRICA

Version 1.0 / 26 October 2012

Date of Clarification Memorandum: 21 August 2013

The items clarified in this Clarification Memorandum (CM) have been approved by the DAIDS Medical Officer and are to be implemented immediately upon issuance. IRB/EC approval of this CM is not required by the sponsor; however, investigators may submit the CM to the IRB/EC overseeing the study at their site for information. This CM is official HPTN 071 documentation and is effective immediately.

This CM and all related IRB/EC correspondence must be retained in the site regulatory file and in other pertinent files. Protocol registration approval is not required by DAIDS for CMs.

This CM includes a minor clarification in the informed consent form.

If the full HPTN 071 protocol is amended in the future, the changes in this CM will be incorporated into the next version of the protocol.

Summary of Revisions and Rationale

This CM serves to modify or clarify the following:

1) Update the protocol team roster
2) Update the study timelines
3) Modify *Population Cohort* exclusion criteria
4) Clarify laboratory processes, procedures, and timelines
5) Update statistical tables

Changes in the protocol are summarized below by section. Added text appears in **bold face** and deleted text appears with a ~~strike through~~.

Protocol Team Roster

Yaw Agyei
International HPTN Network Lab QA/QC Coordinator
Dept. of Pathology
Johns Hopkins Univ. School of Medicine
Pathology Building, Room 313
600 North Wolfe Street
Baltimore, MD 21287, USA
Phone: +27-813766180/+001-410-614-6736
Email: yagyei1@jhmi.edu

Mark Barnes
HPTN Ethics Working Group Representative
Partner, Ropes & Gray LLP
Lecturer, Harvard Law School
Prudential Tower, 800 Boylston Street
Boston, MA 02199-3600Phone: +001-617-951-7827
Email: mark.barnes@ropesgray.com

Nulda Beyers
Clinical Scientist/Site Principal Investigator
Desmond Tutu TB Centre
Stellenbosch University
Francie van Zijl Avenue
Clinical Building, K floor, Room 0065
Tygerberg Campus
Western Cape, 7505, South Africa
Phone: +**21-**21 938 9114
Fax: + **27-**21 938 9719
Email: nb@sun.ac.za

Vanessa Cummings
HPTN NL QC Representative
Dept. of Pathology
Johns Hopkins Univ. School of Medicine
Pathology Building, Room 313
600 North Wolfe Street
Baltimore, MD 21287, USA

Phone: +001-410-502-5296/410-614-0479
Fax: +001-410-614-0430/410-614-6739
Email: vcummin1@jhmi.edu

~~Corey Kelly~~
~~*Project Manager*~~
~~SCHARP-FHCRC~~
~~1100 Fairview Ave. North, E-129~~
~~PO Box 19024~~
~~Seattle, WA 98109, USA~~
~~Phone: 206-667-5170~~
~~Fax: 206-667-4812~~
~~E-mail: ckelly@scharp.org~~

Elizabeth Greene
Clinical Research Manager
FHI360
2224 E NC Hwy 54
Durham NC 27713, USA
Phone: +001-919-544-7040 ext. 11124
Email: egreene@fhi360.org

Katie McCarthy
Clinical Research Manager
FHI360
2224 E NC Hwy 54
Durham, NC 27713
Phone: +001-919-544-7040 ext. 11439
Email: kmccarthy@fhi360.org

Ayana Moore
~~*Senior Clinical Research Manager*~~ ***Scientist***

Maurice Musheke
Investigator
ZAMBART
University of Zambia
School of Medicine, Ridgeway Campus
Lusaka, Zambia
Phone: +260 211 254710, 260 211257215
Fax: +260 211 254710
Email: Maurice@zambart.org.zm

Albert Mwango
Investigator
ZAMBART
University of Zambia
School of Medicine, Ridgeway Campus
Lusaka, Zambia
Phone: +260 211 254710, 260 211257215
Fax: +260 211 254710
Email: albert.mwango@moh.gov.zm

Alwyn Mwinga
Investigator
ZAMBART
University of Zambia
School of Medicine, Ridgeway Campus
Lusaka, Zambia
Phone: +260 211 254710, 260 211257215
Fax: +260 211 254710
Email: Alwyn@Zambart.org.zm

Monde Muyoyeta
Investigator
ZAMBART
University of Zambia
School of Medicine, Ridgeway Campus
Lusaka, Zambia
Phone: +260 211 254710, 260 211257215
Fax: +260 211 254710
Email: Monde@zambart.org.zm

Musonda Simwinga
Investigator
ZAMBART
University of Zambia
School of Medicine, Ridgeway Campus
Lusaka, Zambia
Phone: +260 211 254710, 260 211257215
Fax: +260 211 254710
Email: Musonda@zambart.org.zm

Shauna Wolf
HPTN NL QC Representative
Dept. of Pathology
Johns Hopkins Univ. School of Medicine
Pathology Building, Room 313
600 North Wolfe Street

Baltimore, MD 21287, USA
Phone: +001-410-502-5296/410-614-0479
Fax: +001-410-614-0430/410-614-6739
Email:* *swolf14@jhmi.edu

Schema

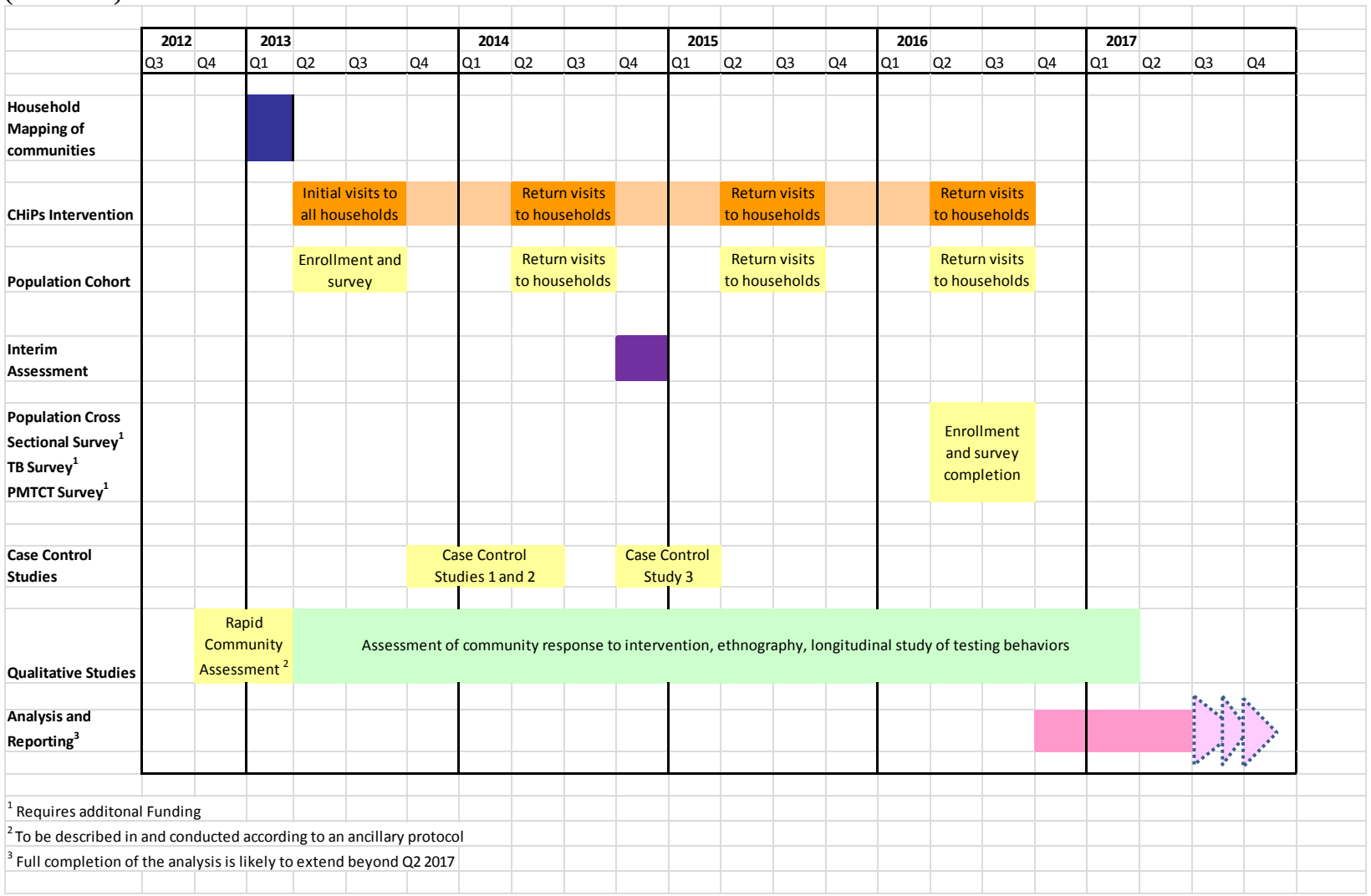
Secondary Objectives:

- Measure the impact of the two intervention packages on the following:
    - Case ~~notification~~ **recording and reporting** rate of tuberculosis

Overview of Study Design and Randomization Scheme

• Health Center Data: TB ~~notification~~ **recording and reporting** and mortality rates

(DELETE)

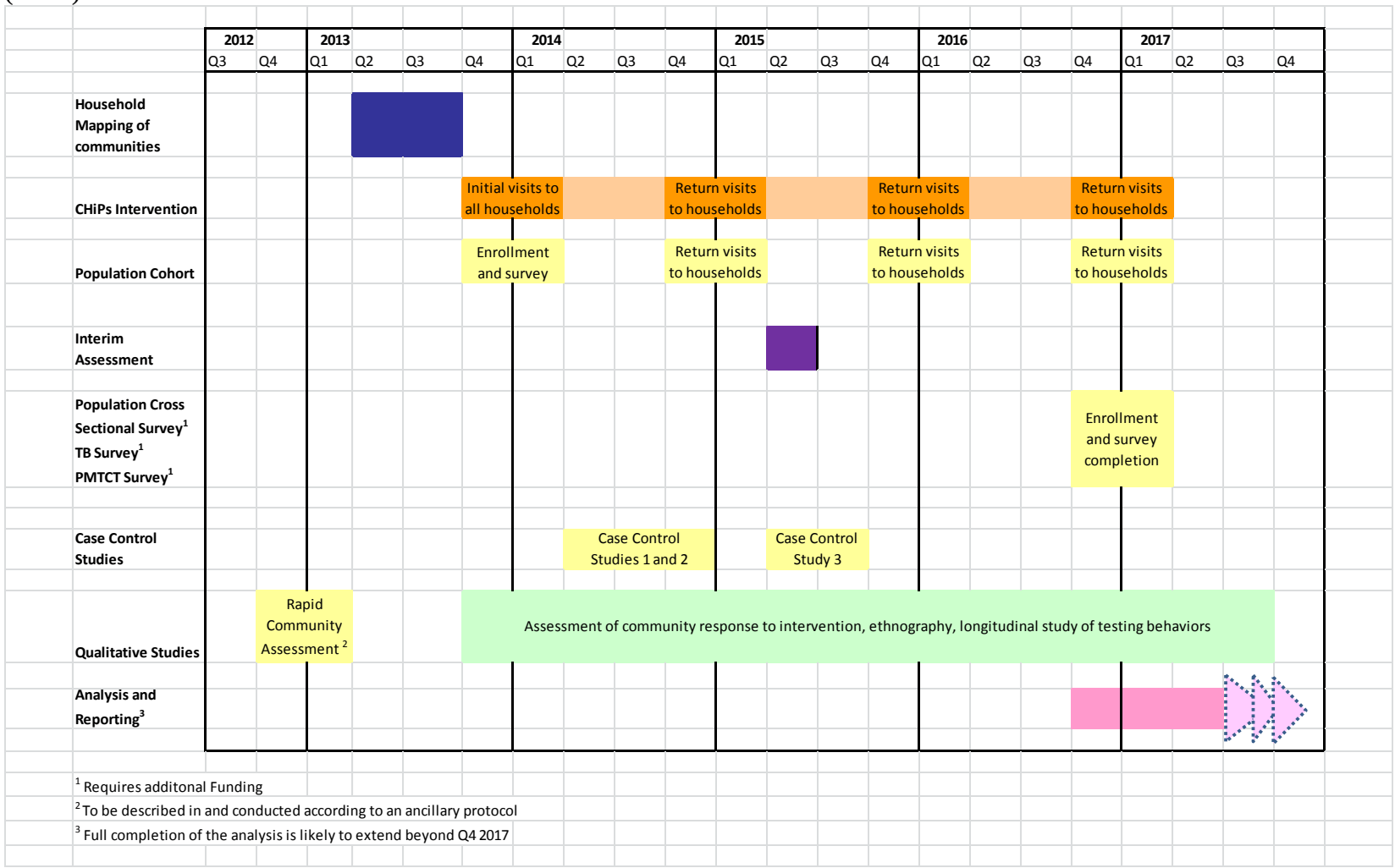


[1] Requires additonal Funding

[2] To be described in and conducted according to an ancillary protocol

[3] Full completion of the analysis is likely to extend beyond Q2 2017

(ADD)


2012
2013
2014
2015
2016
2017
Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4
Household Mapping of communities
CHiPs Intervention
Initial visits to all households
Return visits to households
Return visits to households
Return visits to households
Population Cohort
Enrollment and survey
Return visits to households
Return visits to households
Return visits to households
Interim Assessment
Population Cross Sectional Survey[1]
TB Survey[1]
PMTCT Survey[1]
Enrollment and survey completion
Case Control Studies
Case Control Studies 1 and 2
Case Control Study 3
Qualitative Studies
Rapid Community Assessment [2]
Assessment of community response to intervention, ethnography, longitudinal study of testing behaviors
Analysis and Reporting[3]
[1] Requires additonal Funding
[2] To be described in and conducted according to an ancillary protocol
[3] Full completion of the analysis is likely to extend beyond Q4 2017

Section 2.2 – Secondary Objectives

- Measure the impact of the two intervention packages on the following:
    - Case ~~notification~~ **recording and reporting** rate of tuberculosis

Section 5.1.3 – Exclusion Criteria *Population Cohort*

- Current ~~or planned~~ enrollment in another HIV treatment~~,~~ **or** prevention~~, or PrEP~~ study
- Current~~, planned~~ or **any** prior enrollment in an HIV vaccine study
- Anything that, in the opinion of the investigator **or designee**, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

Section 5.2.4 – [*Population Cohort*] Procedures and Activities

Laboratory Procedures*

- HIV confirmatory testing (if indicated)
- Plasma storage*****

Section 5.5.1 – Tuberculosis Case Notification

Section 5.5.1 – Tuberculosis Case ~~Notification~~ **Recording and Reporting**

In all of the study communities, the TB ~~notification~~ **recording and reporting** process will be strengthened by the use of additional diagnostic tests and enhanced monitoring of the TB case registration system.

Data from this system will be compiled at regular intervals during the trial and used to measure the following outcomes:

- ~~Notification~~ **Recording and reporting** rate of bacteriologically confirmed pulmonary tuberculosis

Table 4

~~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%~~

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)**	**61%**	**25%**	**63%**	**27%**
	Impact on cumulative incidence (2 first years)	**58%**	**24%**	**61%**	**25%**
	Impact on HIV incidence during Year 1	**51%**	**20%**	**54%**	**21%**
	Impact on HIV incidence during Year 2	**65%**	**27%**	**67%**	**28%**
	Impact on HIV incidence during Year 3	**67%**	**29%**	**68%**	**30%**
South Africa	**Impact on cumulative incidence (3 years)**	**62%**	**26%**	**64%**	**27%**
	Impact on cumulative incidence (2 first years)	**59%**	**25%**	**61%**	**26%**
	Impact on HIV incidence during Year 1	**52%**	**22%**	**55%**	**23%**
	Impact on HIV incidence during Year 2	**65%**	**28%**	**67%**	**29%**
	Impact on HIV incidence during Year 3	**68%**	**29%**	**69%**	**30%**

Table 5

~~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%~~
~~South Africa~~	~~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%~~

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%**	**24%**	**60%**	**25%**
	Impact on cumulative incidence (2 first years)	**53%**	**21%**	**56%**	**22%**
	Impact on HIV incidence during Year 1	**42%**	**16%**	**45%**	**17%**
	Impact on HIV incidence during Year 2	**64%**	**27%**	**66%**	**28%**
	Impact on HIV incidence during Year 3	**68%**	**29%**	**69%**	**31%**
South Africa	**Impact on cumulative incidence (3 years)**	**59%**	**25%**	**61%**	**26%**
	Impact on cumulative incidence (2 first years)	**54%**	**23%**	**57%**	**24%**
	Impact on HIV incidence during Year 1	**44%**	**18%**	**47%**	**19%**
	Impact on HIV incidence during Year 2	**64%**	**27%**	**67%**	**29%**
	Impact on HIV incidence during Year 3	**68%**	**30%**	**70%**	**31%**

Table 7

HIV incidence rate/ 100py (control arm)	Between-cluster coefficient of variation (k)	Effectiveness (%) Arm A	Effectiveness (%) Arm B	Power (%)
1.0	0.15	50%	20%	89%
1.0	0.15	50%	25%	78%
1.0	0.15	55%	25%	92%
1.0	0.15	55%	30%	82%
1.0	0.15	60%	25%	98%
1.0	0.15	60%	30%	94%
1.0	**0.15**	**65%**	**25%**	**99%**
1.0	**0.15**	**65%**	**30%**	**99%**
1.0	0.20	50%	20%	78%
1.0	0.20	50%	25%	65%
1.0	0.20	55%	25%	83%
1.0	0.20	55%	30%	71%
1.0	0.20	60%	25%	93%
1.0	0.20	60%	30%	87%
1.0	**0.20**	**65%**	**25%**	**98%**
1.0	**0.20**	**65%**	**30%**	**96%**
1.5	0.15	50%	20%	94%
1.5	0.15	50%	25%	86%
1.5	0.15	55%	25%	96%
1.5	0.15	55%	30%	90%
1.5	0.15	60%	25%	99%
1.5	0.15	60%	30%	98%
1.5	**0.15**	**65%**	**25%**	**99%**
1.5	**0.15**	**65%**	**30%**	**99%**
1.5	0.20	50%	20%	84%
1.5	0.20	50%	25%	72%
1.5	0.20	55%	25%	88%
1.5	0.20	55%	30%	78%
1.5	0.20	60%	25%	96%
1.5	0.20	60%	30%	92%
1.5	**0.20**	**65%**	**25%**	**99%**
1.5	**0.20**	**65%**	**30%**	**98%**

Section 7.1.3 – Secondary Endpoints

(2) Community Viral Load 12, 24, and 36 Months after the Start of Intervention
At 12 and 36 months, viral load will be measured in **approximately** 75 HIV-infected individuals in each community (subject to funding for HIV viral load testing).

Section 7.4.1 - HIV Incidence

Data on estimated HIV incidence in the control arm (Arm C) based on the 12 month follow-up of the *Population Cohort* will be presented to the DSMB. These data will be prepared by a statistician independent of the study team so that they are not inadvertently unblinded to data on the effect size after 12 months. The DSMB will evaluate the implications of this incidence estimate on study power and will consider whether any change in the duration of the study would be appropriate. **Note that results from the 12-month survey may not be available for a considerable time after sample collection is completed. This is because of the very large sample size of the PC, the need to perform HIV testing both in-country and at the HPTN NL, and the need to complete QA testing including confirmation of HIV seroconversion, prior to data analysis.**

Section 7.6 - Outcomes for Secondary Objectives

- Community viral load (if funding is available)
    - Viral load in HIV-infected members of the *Population Cohort* (**approximately** 75 per cluster, randomly-selected) at enrollment, 12 months, and 36 months

NB - Viral load/drug resistance testing will be performed at the 24 month visit, as a measure of treatment adherence, among HIV infected members of the *Population Cohort*, rather than delaying to 36 months. If the 24 month data on this indicates a significant number of participants not virally suppressed/with drug resistance, then additional funding may be sought to analyse these data again at 36 months in the *Population Cohort* and/or the *Population Cross Sectional Survey*. **Data from the 24 month visit will not be available until some time after the study ends.**

- Case ~~notification~~ **recording and reporting** rate of tuberculosis
    - Case ~~notification~~ **recording and reporting** rates of bacteriologically-confirmed TB diagnosed among the general population of patients seeking care at health centers as recorded by health centers

Section 7.11 – Tabular Summary of Outcomes [Table 10]

Community viral load [a]
*Viral load in a subset of **approximately** 75 HIV-infected cohort/survey members per community*

ART drug resistance [a]
ART resistance testing may be performed on samples from enrollment, 12 month, and 24 month visits among cohort members initiating ART after intervention roll-out~~, who have detectable viral load at 36 month~~ (pending funding)

Case ~~notification~~ **recording and reporting** rate of tuberculosis
*Case ~~notification~~ **recording and reporting** rates of bacteriologically-confirmed TB diagnosed among health center attendees as recorded by health centers*

Section 9.1 – Local Laboratory Specimens

"Local Laboratory" in this study refers to regional laboratories and centralized laboratories in each country. Laboratory testing will be performed using stored samples to meet study objectives. ~~In most cases, t~~ **The** results of testing performed using stored samples will not be returned to study sites or participants. The HPTN NL will determine the location of testing. Tests performed by Local Laboratories are described in more detail in Appendix I and the SSP Manual. **Local Laboratories performing these tests will receive External Quality Assurance (EQA) panels for HIV and HSV-2 testing from the HPTN NL.** ~~Local Laboratories performing these tests must demonstrate successful participation in relevant External Quality Assurance (EQA) programs. The EQA results may be monitored by Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) at the discretion of the HPTN NL.~~

Population Cohort:

- Blood specimen for the following:
  - HIV testing
  - Plasma **storag**e
  - HSV-2 testing

Section 9.4 – Specimen Storage and Possible Future Research Testing

Study site staff will store plasma collected in this study until all protocol-related testing is complete. Note that some testing will be performed retrospectively, after the last participant completes the final study visit. Protocol testing will include QC testing and other testing performed at or coordinated by the HPTN NL. **The study site will ship specimens to the HPTN NL on a routine basis, and will ship additional specimens as requested by the HPTN NL. Additional information will be provided in the SSP Manual.** ~~The study site will be informed by the SDMC when shipments to the HPTN NL are required, and will be instructed which samples to ship.~~ Stored samples may also be used to evaluate methods for cross-sectional HIV incidence determination, to evaluate the linkage of HIV infections, to characterize HIV viruses (e.g., HIV genotyping, HIV subtyping, HIV sequencing and phylogenetics, HIV tropism), and to evaluate the host response to HIV infection. Testing may also be performed to evaluate the presence of antiretroviral drugs **and other substances** in study samples.

Appendix I - Schedules of Study Visits and Procedures

Footnotes for the *Population Cohort*

[2] Plasma samples will be stored at an in-country centralized laboratory. Stored samples will be used for testing at one or more centralized laboratories and at the HPTN Network Laboratory in the U.S. Some testing may be performed at other laboratories in the US at the discretion of the HPTN Network Laboratory. Testing performed on stored samples will not be performed in real-time. **Results will not be returned to study sites or participants. The study site will ship specimens to the HPTN NL on a routine basis, and will ship additional specimens as requested by the HPTN NL. Additional information will be provided in the SSP Manual.** ~~In most cases, results will not be returned to study sites or participants. Samples will be shipped to the HPTN NL on request.~~

[7] Additional testing will be performed at the HPTN NL or at another laboratory at the discretion of the HPTN NL. Retrospective HIV testing will be performed for quality assurance and to determine HIV prevalence and HIV incidence. This may include testing related to cross-sectional assessment of HIV incidence. Results from this testing will not be returned to study participants; they will have access to HIV diagnostic testing during the home visit and at the health centers. Quality assurance testing may also be performed to evaluate in-country HSV-2 testing. A subset of samples may also be used to characterize the HIV virus and the host response to HIV infection, to analyze linkage of HIV infections, or to measure/detect the presence of antiretroviral drugs **or other substances in samples. Results will not be returned to study sites or participants** ~~in samples~~.

Appendix II - Sample Informed Consent Form – Population Cohort

What will happen during this study?

- Collect up to 15 mL blood (about 3 teaspoons) for HIV testing and other HIV-related tests as well as herpes simplex-2 testing. Some blood will be stored for **other** study-related testing.

Appendix VII – Sample Size Calculations

(3B) Community viral load 12 and 36 months after start of intervention

N=**approximately** 75 HIV-positive individuals in each community