

**SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:**

HPTN 071:

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

Version 1.0 / 26 October 2012

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Final Version 2.0 / 02 June 2015

Non-IND Study

Information/Instructions to Study Sites from the Division of AIDS

Prior to implementing the changes in this amendment, HPTN 071 study sites will submit this Summary of Changes, Version 2.0 of the protocol, and new informed consent forms, to all relevant regulatory authorities and Institutional Review Boards (IRBs). Once approved by the relevant regulatory authorities and IRBs, the changes in this amendment should be implemented, including immediate use of new informed consent forms.

The amended protocol and revised informed consent forms must be registered with the DAIDS Protocol Registration Office after IRB approval is obtained; however, implementation of the changes, including use of new informed consent forms, should not wait for registration.

File this Summary of Changes, Version 2.0 of the protocol, corresponding site-specific informed consent forms, and all associated IRB correspondence in your essential document files for HPTN 071.

SUMMARY OF REVISIONS AND JUSTIFICATION

Summary of Significant Revisions

This protocol amendment includes many revisions to version 1.0 of the protocol, some of which are minor or administrative in nature. The most significant revisions are highlighted in the list below.

- Incorporate changes previously approved in Clarification Memos #1 and #2. Such changes are identified below as 'CM#1' or 'CM#2'. Changes first introduced with this amendment are labeled 'Current revision'.
- Update the study timeline.
- Clarify laboratory nomenclature, processes, procedures and timelines.
- Revise the Human Subjects Considerations section and the sample informed consent form for Arm A participants starting art immediately to address suggestions from the Protection of Participants, Evaluation, and Policy Branch at DAIDS.
- Clarify in the CHiPs Information Sheet which activities of the CHiPs intervention are being consented to through individual informed consent.
- Allow parents or guardians to consent for the minors in their charge to participate in the intervention activities requiring individual informed consent through the addition of appropriate language in the CHiPs Information Sheet.
- Clarify that portions of some samples collected from *Population Cohort (PC)* participants will be used for an ancillary *Phylogenetics Ancillary Study*, if funding for this ancillary study is obtained, if the participant agrees to this use through a separate informed consent process described in the ancillary study protocol, and if uses of the samples for main study objectives are complete.

General Revisions

- Updates were made to the title page, table of contents, list of tables and figures, list of abbreviations and acronyms, protocol team roster, Investigator of Record page, and references. (Current revision)
- References to the HPTN 'Network Lab' (NL) were changed to refer to the 'HPTN Laboratory Center' (LC) throughout the protocol due to a name change. (Current revision).
- In CM#1 to the protocol, the phrase 'case notification' had been changed to 'case recording and reporting'. This decision has subsequently been reversed and the language revised back to 'case notification' in the current document.
- Throughout the protocol, 'health care facilities' was changed to 'healthcare facilities', 'ART drug resistance' was changed to 'ARV drug resistance', and 'CD4 count' was changed to 'CD4 cell count'. (Current revision)

- Throughout the protocol, references to health practices that would be performed according to ‘national guidelines’ were changed to ‘local guidelines’. Implementation of changes to national guidance often proceeds in a phased manner, and clinic practice may only match revised national guidelines once these are initiated by the Ministry/Department of Health in their community. (Current revision)
- For all sample informed consent forms (Appendices II-IV), language was added to clarify that it is expected that sample informed consent forms will be modified to meet local requirements including those of local ethics committees and that modifications made locally to prior versions of the consents, that have already been approved for use in-country, are expected to be maintained in subsequent site-specific consent versions.

Protocol Team Roster

- Yaw Agyei, Mark Barnes, Vanessa Cummings, Elizabeth Greene, Katie McCarthy, Maurice Musheke, Albert Mwangi, Alwyn Mwinga, Monde Muyoyeta, Musonda Simwina, and Shauna Wolf were added to the protocol team roster. (CM #1)
- Corey Kelly was removed from the protocol team roster. (CM #1)
- Lisa Bunts, Anne Cori, Graeme Hoddinott, Mohammed Limbada and Michael Pickles were added to the protocol team roster. (Current revision)
- Nathaniel Chishinga, Elizabeth Greene, Katie McCarthy, and Maurice Musheke were removed from the protocol team roster. (Current revision)
- The telephone number for Nulda Beyers was corrected. (CM #1)
- The titles for Peter Bock, Vanessa Cummings, Ayana Moore, Albert Mwangi, Alwyn Mwinga, Monde Muyoyeta, Musonda Simwina, Peter C. Smith were corrected. (CM #1 and current revision)
- The business address for FHI360 staff members was updated. (Current revision)

Schema and Overview of Study Design and Randomization Scheme

- A note was added to the Schema indicating that sample sizes for proposed but unfunded surveys may change. (Current revision)
- In The Overview of Study Design and Randomization Scheme, the word ‘assays’ was changed to ‘assessments’, the abbreviation ‘NB’ was replaced with the word ‘Note’ and the number of districts in Zambia involved in the protocol was corrected from 5 to 6. (Current revision)

Section 1.2.4 – Innovation

- Language was updated to reflect the most recent announcement about the START trial.
- A paragraph concerning the effects of the PopART intervention upon TB in the community was moved and slightly modified because the team is study team is now

pursuing funding for a TB ancillary/substudy separately from (rather than as a part of) the main HPTN 071 protocol. (Current revision)

Section 2.2 – Secondary Objectives

- Reference to Table 7 was deleted. (Current revision)

Section 2.4 - Timing of Deployment of Intervention and Research Components

- The time necessary for completion of the first year of intervention deployment was revised to one year from six months. Language about the relative timing of *Population Cohort* visits and CHiPs visits, and reference to pursuit of funding for an additional TB study was removed. (Current revision)
- The primary outcome analysis and reporting timeline description was clarified, and justification was added for the current timeline predictions. (Current revision)
- Figure 2 was revised to reflect current expectations for the timing of study components. (CM #1 and Current revision)

Section 2.5 - Cross-Sectional HIV Incidence Estimation

- The algorithm for HIV incidence estimation for subtype B HIV was revised from a BED capture immunoassay [BED-CEIA] algorithm to a limited antigen avidity assay and a description of an alternate multi-assay algorithm was added. The discussion on applying multi-algorithm assays to incidence estimation for subtype C HIV was revised for clarity. (Current revision)

Section 3.2- Description of CHiP Teams

- It was clarified that CHiPs teams will consist of two people but will not necessarily be gender-balanced. (Current revision)

Section 3.3- Universal HIV Testing and Linkage to Care

- Language was modified to accurately reflect the amount of time needed to complete CHiPs testing round on. (Current revision)
- It was clarified that HIV rapid testing procedures will follow local guidelines. (Current revision)
- Language was modified to reflect more accurately how follow-up is being done in the CHiPs intervention and to remove no longer accurate language about creation of a local community HIV database. (Current revision)

Section 3.4- Male Circumcision

- Language about the potential use of novel devices for male circumcision was removed. (Current revision)

Section 3.5- Universal Treatment (Arm A)

- Language was added to reinforce that immediate treatment for HIV is offered in Arm A communities, with informed consent. (Current revision)
- Language was added to clarify reasons and frequency of CHiPs' follow-up visits to households. (Current revision)

Section 3.7- Prevention of Mother-to-Child Transmission

- Language was added to clarify that all HIV infected pregnant or breastfeeding women are eligible for lifelong ART per government policy and Zambia and the Western Cape of South Africa. (CM #2)

Section 3.9- Screening and Referral for TB

- A new sub-section was added describing CHiPs activities for screening and referral for TB. (Current revision)

Section 3.12.1- Activities with Local Health Centers/Community Institutions

- Language about use of data systems to identify CHiPs clients who should be followed up regarding referrals was modified. (Current revision)
- Language was consolidated regarding types of voluntary counseling and testing for HIV to be promoted as part of the intervention. (Current version)

Section 3.12.2- Collaborations

- Table 1 was updated slightly to reflect changes described above for Section 3. (Current revision)

Section 4.1 – Description/Selection of the 21 Study Communities

- Language about future selection of sites was removed to reflect the fact that sites are already chosen and the study underway. (Current revision)

Section 5.1.1 – Sampling/Recruitment of Population Cohort

- Language was added to clarify that households will be randomly selected for participation in the Population Cohort, and that field staff will not solicit enrollment into the Population Cohort of community members living in the same household as an employee of Zambart of the Desmond Tutu TB Center. (CM #2)

Section 5.1.3 – Exclusion Criteria Population Cohort

- Exclusion criteria for the Population Cohort were modified to remove 'planned' enrollment in certain types of HIV studies. (Current revision)

Section 5.1.4 - Procedures and Activities *Population Cohort*

- Completion of eligibility assessment was added as a *Population Cohort* creation activity. (Current revision)

- Language regarding activities to assess stigma and discrimination was revised. (Current revision)
- HIV and HSV-2 testing were added under Laboratory procedures, and reference to Appendix IA was added. (Current revision)
- A note was added to indicate that in communities where there is a shortfall of ~20% or more in Population Cohort enrollment by the end of the first year, additional participants may be enrolled in the next 12-month period. (Current revision)
- A description of how stored samples will be used for retrospective centralized testing was deleted and replaced with reference to Section 9 of the protocol. Reference to the *Phylogenetics Ancillary Study* protocol and HPTN 071 SSP were added. Language was added to make it clear that although laboratory results are not routinely returned to participants, discrepant HIV test results will trigger a return by staff to a participant to encourage them to seek additional testing. (Current revision)

Section 5.1.5 - Reviewing Health Center Records for *Population Cohort*

- A slight modification was made to language regarding use of health center records. (Current revision)

Section 5.1.6 - Retention in *Population Cohort*

- Because this is not a clinic-based trial, there are not scheduled visits, and so a procedure to follow up on missed visits was removed. (Current revision)
- Language regarding how data from participants who move within a community may be used for analysis was updated. (Current revision)

Section 5.2.4 - Procedures and Activities *Population Cross-Sectional Survey*

- An erroneous asterisk was deleted. (CM #1)
- HIV testing was added under Laboratory Procedures, and HIV confirmatory testing was deleted. A description of how stored samples will be used for retrospective centralized testing was deleted and replaced with reference to Section 9 of the protocol. Reference to the *Phylogenetics Ancillary Study* protocol and HPTN 071 SSP was also added. (Current revision)

Section 5.3 and Sub-Sections - Case-Control Studies

- An exclusion criterion was added to indicate that staff and the members of their household are excluded from participating in case control studies. (Current revision)
- Cases and controls in case control study 2 will be divided based upon whether they started ART within 6 months of being identified as HIV-infected and referred for HIV care by CHiPs, rather than within 3 months of testing HIV positive. This reflects a change throughout this section to allow more time for clients to initiate care and a

recognition that some of the clients CHiPs will refer to care will have tested positive for HIV before CHiPs arrival at their household. (Current revision)

- Language was changed in this section to describe initiation of care within the specified window as ‘timely’ rather than ‘immediate’. (Current revision)

Section 5.6 - Proposed Additional Surveys

- A paragraph regarding addition of a TB survey to the 071 trial was removed since this will now be pursued as an independent ancillary study. This involved removal also of the TB item from Table 3 and removal of appendix IX from the protocol, so the appendix describing the hoped-for PMTCT ancillary became appendix IX.(Current revision)

Section 5.7 - Comparative Table of Study Activities across All Study Arms

- Language in Table 3 was clarified regarding consent of minors for HIV counseling and testing. (Current revision)

Section 7.1.1 - Mathematical Modeling and Sample Size Calculations

- Tables 4 and 5 were updated. (CM #1)

Section 7.1.2 - Primary Endpoint - HIV Incidence Over 36 Months

- Table 7 was updated. (CM #1)

Section 7.1.3 – Secondary Endpoints

- The abbreviation “NB” was changed to “Note.” (Current revision)
- The word “approximately” was added before the sample size for the community viral load measurements at months 12 and 36. (CM #1)
- Language was added so that the case control study description matches that in earlier parts of the document.

Section 7.4 – Interim Evaluation

- The anticipated date for interim evaluation was updated to reflect current expectations. (Current revision)

Section 7.4.1 - HIV Incidence

- A justification for the timeline of when results may be expected from the 12-month survey was provided. (CM #1)

Section 7.6 - Outcomes for Secondary Objectives

- The word “approximately” was added before the sample size for the community viral load measurements at months 12 and 36. (CM #1)
- The abbreviation “NB” was changed to “Note.” (Current revision)

- Language was added indicating that data from the 24-month visit may not be available until some time after the study ends. (CM #1 and current revision)
- A slight change was made to the description of how HSV-2 incidence will be assessed (Current revision)

Section 7.11 – Tabular Summary of Outcomes

- The word “approximately” was added before the sample size in the table for the community viral load measurements. (CM #1)
- Eligibility criteria of cohort members for ART drug resistance testing were modified. (CM #1)
- ‘If funded’ was added to the descriptions of viral load and resistance study descriptions. Revisions were also made to the description of how resistance and HSV-2 incidence work will be performed (Current version).

Section 8.4 – Fair Subject Selection

- The language describing how the intervention will be provided to different populations in the community was revised and clarified. (Current revision)

Section 8.5.2.3 - Minimizing Risks to Individuals

- Language regarding electronic data collection was updated to reflect additional groups from whom data will be collected and to provide additional detail on how the security of that data is protected. (Current revision)
- The description of the proposed phylogenetics ancillary study was revised, and reference was added to the phylogenetics ancillary protocol. (Current revision)

Section 8.6.3 - Individual Consent

- The sub-section on Individual consent for CHiP team activities was moved to the beginning of the section. (Current revision)
- Language was added to reiterate that participants consenting to commencement of ART regardless of CD4 or clinical stage will still be asked to consent (verbally) to any CHiP team activities and related data collection. (Current revision)
- A change was made to indicate that informed consent for the early initiation of ART will be required for those who are otherwise ineligible per ‘local’ treatment guidelines (instead of “national” guidelines). (Current revision)

Section 8.6.4 - Waiver of Individual Consent to Access CHiP and Routine Clinic Data

- The term “anonymized form” was changed to “coded form.” (Current revision)
- A detailed description of how CHiP intervention participants’ identities will be protected was added. (Current revision)

Section 9.1 - Local Laboratory Specimens

- Language regarding external quality assurance panels for local laboratories was clarified. (CM #1)
- The word “storage” was added after plasma under blood specimens to be collected. (CM #1)
- HSV-2 testing was moved up in order before plasma storage under blood specimens to be collected. (Current revision)

Section 9.2 – Network Laboratory Specimens

- The title of the section was revised to “HPTN Laboratory Center (LC) Specimens.” (Current revision)
- Wording throughout the section was revised for clarity. (Current revision)
- Reference to use of samples for the *Phylogenetics Ancillary Study* was added. (Current revision)
- Language noting that sites will ship specimens to the LC on a routine basis as described in the study-specific procedures manual was moved from section 9.4 to section 9.2. (Current revision)

Section 9.3 – Quality Control and Quality Assurance Procedures

- Language was changed to note that the random sampling of blood samples requested for quality testing purposes will be generated by LC working with HPTN SDMC. (Current revision)

Section 9.4 - Specimen Storage and Possible Future Research Testing

- Language noting that sites will ship specimens to the LC on a routine basis as described in the study-specific procedures manual was added (CM #1) and subsequently moved to section 9.2 (current revision).
- Language that study sites will be informed by the SDMC when shipments to the LC are required was deleted. (CM #1)
- Specific examples of how samples may be used for future testing were deleted, as the examples referred to phylogenetic analyses, and a new section was added (section 9.4.1)

to detail specimen storage for the *Phylogenetics Ancillary Study*. Language was revised slightly for clarity. (Current revision)

Section 9.4.1 - Proposed Phylogenetics Study

- A new section (section 9.4.1 – Proposed Phylogenetics study) was added in order to describe specimen storage specifically for the *Phylogenetics Ancillary Study*. (Current revision)

Appendix I - Schedules of Study Visits and Procedures

- The Laboratory Procedures section of the Appendix IA table was revised and simplified to include HIV testing, HSV-2 testing, and Plasma storage only, mirroring sections 5 and 9 of the protocol. (Current revision)
- The footnotes to the Appendix IA table were revised to be consistent with the revised table, and some wording was revised for clarity. A footnote regarding the soliciting of consent for the Phylogenetics Ancillary study was added. Some changes that were added in CM #1 were subsequently revised in the current revision. (CM #1 and current revision)

Appendix V - Sample Informed Consent Form – Arm A Participants Starting ART Immediately

- The wording in the section “What are the potential benefits?” has been revised slightly in light of results from the START trial that strengthen the evidence that initiating ART early has clinical benefit for the health of HIV-infected patients.
- The section on reasons why a participant may be withdrawn from the study without their consent was revised. The word “activity” in the section title was deleted and replaced with the word “study.” The reasons originally given for withdrawal from the study (the study is stopped or the study may be harmful to the participant or others) were deleted and replaced with a paragraph informing the participant that the only study activity is early ART initiation. It clarifies that if the study stops or is ended, the participant will not be taken off of ART; rather, the participant will only be taken off of ART if it is his or her own choice or is recommended by a provider. (Current revision)

Appendix VI - Sample Informed Consent Form – CHiP Team Activities (Subject Information Sheet)

- Additional language was added to explain further how confidentiality of data held on the electronic device are protected. (Current version)
- Language was revised to clarify which activities of the CHiPs intervention will only be offered to individuals who have provided individual informed consent, and which activities will be offered to all members of the household. Language was added to allow parents or guardians to consent for the minors in their charge to also participate in the activities requiring individual informed consent. (Current revision) *Note:* Local ethics review committees will be asked to specify the age at which assent from minors will be required for these activities and how that assent should be obtained.

- Language was added that household members may choose not to receive any services recommended by the CHiPs without penalty. (Current revision)

Appendix VII – Sample Size Calculations

- The word “approximately” was added before the sample size for the community viral load measurements. (CM #1)

Appendix VIII - Population Cross-Sectional Survey

- The word “proposed” was added before the word “Population” in the title and in the table on Schedule of Study Visits and Procedures, so that it reads “Proposed Population Cross-Sectional Survey,” to reflect that funding is still pending for this survey. (Current revision)
- In the last outcome for secondary objectives, “schedule of events” was deleted and replaced by “Section 9” to reference where information on other testing with stored samples may be found. (Current revision)
- The Schedule of Study Visits and Procedures was revised for clarity. Under Laboratory Procedures, HIV viral load testing, HIV resistance testing, and other testing were deleted from the table. HIV testing was moved up in order to be first and “using stored samples” was deleted, and the word “for” was deleted from the phrase “plasma for storage.” (Current revision)
- The footnotes for the Schedule of Study Visits table were revised to be consistent with revisions in Appendix IA. (Current revision)

Appendix IX – PMTCT Survey

- The word “proposed” was added before the word “PMTCT” in the title and in the table on Schedule of Study Visits and Procedures, so that it reads “Proposed PMTCT Survey,” to reflect that funding is still pending for this survey. (Current revision)