

Letter of Amendment # 3 to:

HPTN 078: Enhancing Recruitment, Linkage to Care and Treatment for HIV-Infected Men Who Have Sex with Men (MSM) in the United States
Version 1.0, dated 8 October 2015
DAIDS Document ID: 11995

Final Version of LoA # 3: 23 June 2016

The following information impacts the HPTN 078 study and must be forwarded to all responsible Institutional Review Boards (IRBs) as soon as possible for their information and review. This Letter of Amendment (LoA) must be approved by all responsible IRBs before implementation.

The information contained in this LoA impacts the sample screening informed consent form (ICF).

Upon receiving final IRB approval for this LoA and the revised screening ICF, sites should implement the LoA immediately. Sites are still required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with the LoA and any IRB correspondence should be retained in the site's regulatory files.

If the HPTN 078 protocol is amended in the future, this LoA will be incorporated into the next version. Deletions to the protocol text are indicated by ~~strikethrough~~; additions are indicated in **bold**.

Summary of Revisions and Rationale

1. Removes Richard Wolitski from the protocol roster
2. Allows direct recruitment, in addition to recruitment via DC-RDS, for the CM intervention, if enrollment targets are not being met by the fourth month of recruitment, on a site by site basis.
3. Allows the distribution of up to six coupons to seeds only. This revision would allow us to use our seeds twice (first giving them three coupons, and then giving them up to three additional coupons if they have distributed their coupons, but they have not been returned to the site by the recipients). The rationale for making this change for seeds only is that it would limit the number of initiated chains, but improve the chance of chain propagation from those who were chosen as some of the best, well-connected representatives of the local MSM population. All other recruiters would only receive three coupons; thus, all references to the number of coupons have been removed from the protocol. Details about how seeds may be given up to six coupons to distribute will be added to the SSP.

Summary of Revisions and Rationale (continued)

4. Removes the specific reference to ten seeds, as we may release more at some sites.
 5. Allows for the collection of blood for CD4 and VL testing at the S1 visit, if the HIV status of the individual (either via self-report or by rapid test administered outside of the study) is positive. For some sites, this may allow for a more streamlined approach for their screening visit flow for those who are HIV-infected.
 6. Indicates that the collection of social impacts at the S1 visit is not required for seeds.
 7. Revises the Screening ICF to include an explanation that direct recruitment may be used in the study and clarifies that additional blood will be taken for HIV re-testing if the first HIV test is indeterminate
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Implementation

Revision 1

PROTOCOL TEAM ROSTER

- ~~Richard J. Wolitski, PhD~~
~~Senior Advisor for Indicator Monitoring and Program Improvement~~
~~National Center for HIV/AIDS, Viral Hepatitis, STD, & TB Prevention~~
~~Centers for Disease Control and Prevention~~
~~1600 Clifton Road (MS E-07)~~
~~Atlanta, GA 30329~~
~~Phone: 404-639-1939~~
~~Email: rwolitski@cdc.gov~~

Revisions 2, 3, 4, 5 and 6

3.0 STUDY POPULATION

Approximately 2700 sexually active MSM (~675 in each participating city) will be recruited for HIV testing via DC-RDS **and, possibly, direct recruitment**. Out of this cohort, 356 HIV-infected MSM who are not virally suppressed and meet the inclusion and exclusion criteria described below will be enrolled into the CM intervention and SOC control study arms.

3.3 Recruitment Process

DC-RDS will be used to recruit MSM into this study, **to the extent possible**. In this method, **8-10 multiple** seeds will be identified in each city, although not all seeds will necessarily be activated throughout the life of the study. Seeds will be the individuals who begin the recruitment chains; they will be selected to represent a range of characteristics (including ethnic and racial minority status) and because they are well-networked within the population. These seeds will undergo training to become a recruiter. They will then be given ~~three~~ coupons with which to recruit others to the study.

Seeds must meet the inclusion/exclusion criteria of the study and are considered study participants.

As this protocol is testing the ability of DC-RDS methodology to find HIV-positive, virally unsuppressed MSM, DC-RDS recruitment will continue throughout the duration of the enrollment period. However, if enrollment targets are not met by the fourth month of recruitment at any given site, direct recruitment (in addition to DC-RDS) will be allowed on a site-by-site basis in order to fully enroll for the CM intervention investigation. These new participants may be treated as seeds, if a given site still needs to initiate additional recruitment chains. There will be no difference in study procedures between participants recruited via DC-RDS and direct recruitment, except that they may or may not be treated as seeds, and thus, may or may not distribute coupons to others.

All seeds, and subsequent participant/recruiters, must not recruit anyone other than peers they know personally who are MSM. These recruits will come to the site and, if they are eligible and agree to participate, will undergo the study's screening procedures before becoming recruiters themselves. Participants will return approximately two weeks later for a second visit, during which they will be reimbursed for the coupons that were brought back to the clinic by other MSM. During this second visit a post-recruitment questionnaire will be administered to characterize how many people in total were approached in the distribution of the ~~three~~ coupons and the characteristics (e.g., age, race) of those who did and did not accept a coupon.

5.1.1 First Screening Visit (S1)

During the first Screening Visit (S1), participants will be consented for the screening procedures, asked for locator information, to complete several questionnaires (see Appendix II) and to have blood collected for laboratory assessments (HIV, HCV and syphilis) and plasma storage. **If a participant is known to be HIV-positive at the S1 visit (either via self-report or by rapid test administered outside of the study), blood may be drawn for CD4 and VL at this visit instead of at the S2 visit.** In addition, pre- and post-test HIV counseling and HIV and sexually transmitted infection (STI) risk reduction counseling will be provided to all participants, as appropriate. Participants will also be assessed for social impacts that may have occurred during the recruitment process. Each participant will be given instructions about the recruitment process, as well as ~~three~~ coupons for distribution.

5.1.2 Second Screening Visit (S2)

All participants will be asked to return for a second Screening Visit (S2) to receive the results of their HIV, syphilis and HCV tests. Post-test HIV counseling and HIV and sexually transmitted infection (STI) risk reduction counseling will be provided, as appropriate. If an individual is found to be HIV-infected or has discordant or inconclusive HIV test results, blood will be drawn for CD4 and viral load (HIV RNA) testing and additional plasma storage. **If a participant has already had blood drawn for CD4 and VL at the S1 visit, it does not have to be repeated at the S2 visit; however, blood for plasma storage is still required.** They will also undergo a social impact assessment. Additional blood will be collected for HIV testing and plasma storage at the second Screening Visit if the HIV test results from the first Screening Visit were not conclusive. A post-recruitment questionnaire will be administered to anyone distributing coupons.

Blood will not be collected from individuals who tested negative for HIV infection at the first screening visit (i.e., those who did not have reactive or positive HIV test result from the S1 visit).

7.1 Review of Study Design

This study is designed to i) evaluate the utility of deep-chain respondent driven sampling (DC-RDS) for finding HIV-infected MSM who are not virally suppressed, and ii) assess the efficacy of an CM intervention package for linking HIV-infected MSM to care and, ultimately, achieving viral suppression. Approximately 2700 MSM will be identified and recruited (see Sections 7.2.1 and 7.6.1 for definition of recruitment) using a DC-RDS strategy in four cities (~675 per city). We expect that approximately 378 of these will be HIV-infected MSM who are not virally suppressed and that 356 of these will be willing to participate. **If insufficient HIV-infected MSM who are not virally suppressed are recruited through DC-RDS then individuals may be recruited from other sources.** These 356 will be randomized to the CM intervention and SOC control study arms of the study. The CM intervention arm will provide a package designed to enhance linkage to care, antiretroviral treatment (ART) initiation, treatment adherence, and retention in care. The intervention will be delivered by a trained CM. The SOC control arm will provide the SOC for linkage to care, initiation of ART, and treatment. The primary outcome of the study is viral suppression 24 months after enrollment.

7.3 Accrual, Follow-up and Sample Size

We will recruit approximately 2700 men via DC-RDS. We expect that 20% (540) will be HIV-infected MSM and that 70% of those (378) will not be suppressed. These 378 individuals form the pool of individuals eligible for enrollment and randomization. If necessary, more than 2700 MSM will be recruited via DC-RDS to achieve the required sample size for enrollment. Conversely, recruitment will continue until at least 2700 MSM are screened (even after the CM intervention and SOC control arms are fully enrolled), so that the DC-RDS-related endpoints can be fully assessed. **If insufficient numbers of HIV-infected MSM with unsuppressed viral load are recruited through DC-RDS, then such MSM may be recruited from other sources.**

7.6.1 Primary Analysis

To assess the ability of DC-RDS to recruit HIV-infected MSM who are not virally suppressed we will measure the proportion of the men that are recruited by DC-RDS (where recruitment is defined as providing a blood draw for HIV and HIV viral load testing) who are HIV-infected and not virally suppressed. An estimate and a 95% confidence interval (CI) based on RDS methods⁷⁶ will be reported. **MSM recruited via other methods will not be included in this analysis.**

7.6.2 Secondary Analysis

We will divide the (approximately 2700) MSM who are recruited into early and later waves of DC-RDS (the definition of “early” and “late” will be included in the statistical analysis plan). We will use a two sample test of proportions (with standard errors adjusted for RDS sampling;⁷⁶) to compare i) the proportion HIV-infected and ii) the proportion HIV-infected and not suppressed, between the early and later recruits. **MSM**

recruited via other methods will not be included in this analysis. A two-sided alpha level of 0.05 will be used for hypothesis testing.

Appendix I: Schedule of Study Visits, Evaluations and Procedures

	Screening (S1)	Screening (S2)	Enrollment (M0)	ART Initiation	Monthly Contact ¹	Follow-up (M3, M6, M9, M12, M18)	Final (M24)
Administrative and Behavioral Evaluations/Procedures							
Social impact assessment	X*	X			I	X	X
Laboratory Evaluations/Procedures							
CD4 cell count testing	X**	X ⁵		X ⁶		X ⁷	X
HIV viral load testing	X**	X ⁵		X ⁶		X	X

Note: Monthly visits will be defined as a predetermined number of weeks, as described in the SSP. **In addition, in special cases, the S2 and enrollment visits may take place on the same day (see SSP).**

X, all participants; I, CM intervention arm only.

* **Seeds do not undergo social impact assessment at the S1 visit.**

** **If a participant is known to be HIV-positive at the S1 visit, blood may be drawn for CD4 and VL at this visit instead of at the S2 visit.**

⁵CD4 cell count and HIV viral load testing will be performed at the S2 visit for those who are HIV-infected or have discordant/inconclusive HIV test results, **unless already performed at the S1 visit** (see SSP Manual).

Revision 7

FROM SCREENING CONSENT FORM (Appendix IV)

PURPOSE OF THE SCREENING

The purpose of the screening activities is to find sexually active MSM using a technique called “respondent driven sampling” or “RDS.” ~~In respondent driven sampling~~ **RDS**, we ask MSM to refer other MSM they know to come to our clinic for screening.

We plan to screen about 2700 participants from four US cities (approximately 675 in each participating city) within one year. During screening, we will test MSM for HIV, hepatitis C virus and syphilis. We will also ask each MSM to complete a questionnaire. In addition, if we find MSM who are HIV-infected, we may invite them to participate in a study testing whether case manager support can help MSM receive consistent HIV care and routinely take their HIV medication. **If we do not find enough HIV-infected MSM using RDS, we may invite MSM to participate in this study that we find in other ways.**

Screening Visit 1

- We will ask you if you have had any problems because you are a part of this screening, **unless you are a “seed,” meaning that you are one of the first people in the study, and did not receive a coupon from someone in the community.**

- We will collect a small amount of blood (approximately 33 mL = about 6 teaspoons) to test for HIV, hepatitis C virus (HCV) and syphilis. The results of these tests will be available at your next visit. **If you know you are HIV-infected at this visit, additional blood (approximately 14 mL = about 3 teaspoons) will be collected to measure your CD4 cell count and viral load.**

Screening Visit 2

- If you are HIV infected or your HIV infection status isn't clear, we will collect a small amount of blood (approximately 14 mL = about 3 teaspoons) to measure your CD4 cell count and viral load, **if we haven't already done so at the S1 visit.** If you do have HIV infection, these tests tell us how much HIV is in your blood (viral load) and how much the virus has affected your ability to fight the virus (CD4).
- If the results of your HIV tests from the first screening visit do not clearly indicate if you are or are not infected, we will **collect a small amount of blood (approximately 20 mL = 4 teaspoons)** ~~also use the blood collected for additional HIV testing.~~
- **In certain cases, we may give you more coupons and ask you to invite MSM you know to come to the clinic for screening.**