

Letter of Amendment #1 for:

HPTN 078

**Enhancing Recruitment, Linkage to Care and Treatment for HIV-Infected Men Who Have Sex with Men (MSM) in the United States
Version 2.0, dated 3 July 2017**

(DAIDS Document ID 11995)

Final Version of LoA #1: Date: 20 December 2017

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Information/Instructions to Study Sites from the Division of AIDS

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 does *not* impact the sample screening informed consent form (ICF).

Upon receiving final IRB approval for this LoA, sites should implement the LoA immediately. Sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). As part of the registration package, sites must submit the Letter of Amendment Investigatory Signature Page, signed and dated by the Investigator of Record. 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**.

HPTN 078

Enhancing Recruitment, Linkage to Care and Treatment for HIV-Infected Men Who Have Sex with Men (MSM) in the United States

DAIDS Study ID 11995

Protocol Version 2.0, Letter of Amendment #1

20 December 2017

Letter of Amendment Investigator Signature Page

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

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Site Investigator of Record

Signature of Site Investigator of Record

Date

Summary of Revisions and Rationale

Due to the inability to fully enroll 356 participants during the predetermined recruitment timeline, HPTN leadership made the decision to end screening and enrollment on December 15, 2017. Despite multiple changes to the recruitment strategy and a great deal of effort and flexibility at the site level, only 40% of the expected enrollment was randomized into the study.

In order to learn as much as possible from those enrolled, particularly about how to retain and support the study population via the case manager intervention, the decision was made to continue follow-up, but to reduce the follow-up period from 24 to 12 months.

The protocol is being revised to reflect the reduction in follow-up in the following manner:

1. All references to 24-month follow-up have been changed to 12-month follow-up.
2. All references to the 18 and 24-month follow-up visits have been removed.
3. The final study procedures, originally affiliated with the 24-month follow-up visit, are now affiliated with the 12-month follow-up visit.
4. The definition of “retained in care” for purposes of analysis has been changed from four visits over 24 months to two visits over 12 months. The restriction that these two visits take place in separate six-month intervals has been removed.

As some participants have already completed their 12 or 18-month follow-up visits, a “Dear Participant” letter is being used to convey the reduction in follow-up from 24 to 12 months to participants. The “Dear Participant” letter will be initial and dated by participants and attached to their original enrollment informed consent forms. Thus, no changes are being made to the informed consent templates.

Implementation

Revision 1: Shorten participant follow-up from 24 to 12 months

All references to 24-month follow-up are changed to 12-month follow-up in the following protocol sections.

Schema

- The primary outcome of the study is viral suppression, ~~24~~ **12** months after enrollment.
- The overall study duration is ~~60~~ **48** months: 24 months for DC-RDS recruitment and enrollment; ~~24~~ **12** months of follow-up for participants who are randomized into the CM intervention and SOC control study arms; and approximately 12 months after the completion of participant study visits for data analyses, phylogenetic assessments and modeling.

Schema and 2.1 Primary Objectives

- Compare the efficacy of the two study arms (CM intervention vs. SOC control) in achieving durable viral suppression (defined as HIV VL < 200 copies/ml) ~~24~~ **12** months after enrollment.

Schema and 2.2 Secondary Objectives

- Assess linkage to care and retention in care in the two study arms by comparing the 1) proportion of men with at least one care visit within 30 days of enrollment, 2) time to the first care visit, and 3) proportion of men with at least ~~four~~ **two** care visits, (~~one in each six-month interval,~~ with at least 60 days between these visits) over the ~~24~~ **12** months after enrollment.
- Compare the proportion of men with HIV-hepatitis C virus (HCV) co-infection in the two study arms who are linked to care (defined as one care visit within 30 days of enrollment) and who achieve (HIV) viral suppression ~~24~~ **12** months after enrollment.
- Examine the association between baseline behavioral, socio-demographic, and clinical characteristics (including syphilis) of HIV-infected men and viral suppression status for all men screened via DC-RDS and for the men in the two study arms ~~24~~ **12** months after enrollment.
- Compare the two study arms with respect to ART adherence at ~~24~~ **12** months after enrollment and changes in sexual risk behavior, health care utilization, stigma, substance use and mental health from baseline to ~~24~~ **12** months after enrollment.
- Evaluate the feasibility and scalability of the CM intervention by measuring the number of intervention contacts (e.g., text message, email, phone, in person) per participant over ~~24~~ **12** months.

2.5 Study Design

- The primary outcome of the CM intervention phase is viral suppression ~~24~~ **12** months after enrollment.

3.1 Inclusion Criteria

- No current plan to relocate in the ~~24~~ **12** months following enrollment

4.0 Study Intervention

- The CM-to-participant ratio will be approximately 1:42 over the ~~24~~ **12**-month period.
- Figure 2 is revised to refer to 12 (instead of 24) month follow-up.

7.1 Review of Study Design

- The primary outcome of the study is viral suppression ~~24~~ **12** months after enrollment.

7.2.1 Primary Endpoints

- Consistent with the primary study objective to compare the efficacy of the two study arms (CM intervention vs. SOC) in achieving viral suppression (defined as HIV VL <200 copies/ml) ~~24~~ **12** months after enrollment, the following endpoint will be assessed:
 - HIV viral load at ~~24~~ **12** months after enrollment

7.7.2 Secondary Endpoints

- Consistent with the secondary study objective to compare the proportion of men in the two study arms who are linked to care and retained in care the following endpoints will be assessed:
 - Number and time of all care visits from randomization through the end of 24 12-month follow-up
- Consistent with the secondary study objective to compare the proportion of men with HIV-HCV co-infection who are linked to care and who achieve HIV viral suppression 24 12 months after enrollment between the two study arms the following endpoint will be assessed:
 - HCV status at baseline
 - HIV viral load at 24 12 months after enrollment
- Consistent with the secondary study objective to examine the association between baseline behavioral, socio-demographic, and clinical characteristics of HIV-infected men and viral suppression status for all men screened via DC-RDS and for the men in the two study arms 24 12 months after enrollment the following endpoints will be assessed:
- Consistent with the secondary study objective to compare ART adherence at 24 12 months and changes in sexual risk behavior, health care utilization, stigma, substance use and mental health between the two study arms over 24 12 months, the following endpoint(s) will be assessed:
 - Self-reported sexual risk behavior (number of male sexual partners, episodes of UAI, characteristics of 3 most recent partners) at baseline and 24 12 months using a standardized assessment tool
 - ART adherence at 24 12 months
 - Health care utilization at baseline and 24 12 months using a standardized assessment tool
 - Stigma at baseline and 24 12 months using a standardized assessment tool
 - Substance use at baseline and 24 12 months using a standardized assessment tool
 - Mental health at baseline and 24 12 months using a standardized assessment tool

7.3 Accrual, Follow-up and Sample Size

- We expect that 40% of the MSM randomized to the SOC control arm will be linked to care and 70% of those linked to care will be suppressed by 24 12 months following enrollment.⁶ We expect that almost none of those not linked to care will be suppressed. Thus, overall, we expect about 28% of the MSM in the SOC control condition will be suppressed at 24 12 months. In the CM intervention arm we expect to raise the linkage rate to at least 55% and the suppression rate, among those linked, to 85%. Thus, we expect that at least 46% of the MSM in the CM intervention arm will be suppressed at 24 12 months. Table 2 shows the required sample size for an individually randomized trial with 90% power, assuming 10% lost-to-follow-up per year, for various effect sizes. For our target effect size of risk difference of 18% points, we require 356 MSM.
- Table 2 Header: Number needed to be randomized to the CM intervention or SOC control to have 90% power to detect the indicated difference in proportion of those virally suppressed at

24 12 months, assuming $\alpha = 0.05$ (two-tailed), power = 90%, loss to follow-up = 10%/year (overall retention of 80% at the end of 2 years).

- Table 2 Content: Difference in proportion suppressed at 24 12 months between arms¹

7.6.1 Primary Analysis

- Among the HIV-infected MSM who are enrolled and randomized we will compare the rates of viral suppression (defined as HIV VL <200 copies/ml) at 24 12 months after enrollment.
- The analysis will follow the intent to treat principle. If a participant drops out prior to 24 12 months, their viral suppression status at last study assessment will be used in the analysis.

7.6.2 Secondary Analysis

- We will also compare the proportion of MSM who are retained in care (defined as at least ~~four~~ **two**-care visits [~~one in each six month interval~~, with at least 60 days between these visits] over the 24 12 months after enrollment) between the CM intervention and SOC control arm.
- We will build a multiple logistic regression model to examine the associations between viral suppression at 24 12 months (outcome) and various demographic characteristics, sexual risk behaviors and clinical characteristics. Further details will be provided in a separate Statistical Analysis Plan.
- Additional analyses will examine the effect of the CM intervention on various sexual risk behavior, ART adherence, stigma, health care use, substance use and mental health measures over the 24 12-month follow-up. The general approach to these analyses will be to build a regression model (linear, log, or logistic, whichever is appropriate for the scale of the measure) that uses the 24 12-month value of the measure as the outcome (or most recent assessment for participants that drop out prior to 24 12 months) and includes the baseline value of the measure (except for ART adherence, where no baseline value is available) and CM intervention arm as covariates.

10.2 Rationale

- The second primary objective of the study is to measure the impact of the CM intervention upon the proportion of MSM achieving viral suppression after 24 12 months (primary objective), and the time to viral suppression (secondary objective), as well as collecting data on intermediate steps including the proportion linked to care and remaining engaged in care (secondary objective).

10.5.2 Model Parameterization

- Table 4 Content: Number of partners and sex acts, role behavior, condom use at baseline (RDS + CM intervention cohort) and after 24 12 months (CM intervention cohort only), partner characteristics at baseline (RDS + CM intervention cohort)

Revision 2: Remove all references to M18 and M24

All references to the 18 and 24-month follow-up visits have been removed in the following protocol sections.

Schema and 2.2 Secondary Objectives

- Compare the proportion of men in the two study arms who are virally suppressed at 3, 6, **and** 9, ~~12 and 18~~ months after enrollment.

5.5 Follow-up Visits (M3, M6, M9, ~~M12, M18~~)

- Follow-up Visits will take place at Months 3, 6, **and** 9, ~~12 and 18~~ for all participants (CM intervention and SOC control arms).

7.7.2 Secondary Endpoints

- Consistent with the secondary study objective to compare the proportion of men in the two study arms who are virally suppressed (defined as HIV VL <200 copies/ml) at 3, 6, **and** 9, ~~12 and 18~~ months after randomization the following endpoints will be assessed:
 - HIV viral load at 3, 6, 3, 6, **and** 9, ~~12 and 18~~ months after enrollment

7.6.2 Secondary Analysis

- We will also repeat the analysis of HIV viral suppression (described in Section 7.6.1) at 3, 6, **and** 9, ~~12 and 18~~ months of follow-up.

Appendix I: Schedule of Study Visits, Evaluations and Procedures

	Screening	Enrollment (M0)	Monthly Contact ¹	Follow-up (M3, M6, M9, M12, M18)	Final (M24-12)
Administrative and Behavioral Evaluations/Procedures					
Informed consent	X	X			
Release of medical information		X			
Contact/locator information	X	X	I	X	X
Questionnaire administration (see Appendix II)	X	X			X
Recruiter training	X				
Coupon reimbursement	X				
Social impact assessment	X ²		I	X	X
Pre- and post-test HIV counseling, including HIV/STI risk reduction counseling	X	X ³			
Offer of partner HIV counseling and testing		X		X	X
Coupon disbursement	X ⁴				
Case manager (CM) intervention		I	I	I	I
Exit interview					X
Clinical Evaluations/Procedures					
Blood collection	X	X		X	X
Syphilis treatment or referral, if indicated	X	X ⁵			X ⁶
HCV treatment or referral, if indicated	X	X ⁵			
Laboratory Evaluations/Procedures					
HIV testing	X ^{7,9}				
Hepatitis C virus testing	X ⁷				
Syphilis testing	X ⁸				X
CD4 cell count testing	X ⁹			X	X
HIV viral load testing	X ⁹			X	X
Plasma storage ¹⁰		X		X	X

Revision 3: Affiliate all M24 visit procedures with the M12 visit

The final study procedures, originally affiliated with the 24-month follow-up visit, are now affiliated with the 12-month follow-up visit, in the following protocol sections.

3.6 Participant Withdrawal and Early Termination

- Every reasonable effort will be made to complete a final evaluation (M24 12 visit procedures) of participants who terminate from the study prior to Month 24 12, and study staff will record the reason(s) for all withdrawals in participant study records.

5.6 Final Visit (M24 12)

- The Final Visit will take place at Month 24 12.

Appendix I: Schedule of Study Visits, Evaluations and Procedures

- (See correction in Appendix I table above.)

Appendix II: Schedule of Questionnaire Domain Administration

Questionnaire Domain	Screening	Enrollment (M0) (Intervention participants [CM Intervention and SOC control arms])	Final (M24-12) (Intervention participants [CM Intervention and SOC control arms])
Demographics	X		
PrEP/PEP/ART use	X		
HIV testing history	X		
Engagement in LGBT community	X		
Post-recruitment questions*	X		
Health care utilization	X		X
Sexual matrix module / sexual risk behavior	X		X
Stigma	X		X
Substance use and mental health		X	X
Medication adherence			X
Exit Interview Questionnaire			X**

Revision 4: Revise the definition of “retained in care”

The definition of “retained in care” for purposes of analysis has been changed from four visits over 24 months to two visits over 12 months; and the restriction that these two visits take place in separate six-month intervals has been removed, in the following protocol sections.

Schema and 2.2 Secondary Objectives

- Assess linkage to care and retention in care in the two study arms by comparing the 1) proportion of men with at least one care visit within 30 days of enrollment, 2) time to the first care visit, and 3) proportion of men with at least ~~four~~ **two** care visits (~~one in each six-month interval~~, with at least 60 days between these visits) over the ~~24~~ **12** months after enrollment.

7.6.2 Secondary Analysis

- We will also compare the proportion of MSM who are retained in care (defined as at least ~~four~~ **two**-care visits [~~one in each six-month interval~~, with at least 60 days between these visits] over the ~~24~~ **12** months after enrollment) between the CM intervention and SOC control arm.

Dear Participant Letter

December 8, 2017

Dear HPTN 078 Study Participant:

We are writing to share new information with you about HPTN 078. HPTN 078 is a study designed to answer two questions.

- What is the best way to find men who have sex with men (MSM) and transgender women who are HIV-infected and not virally suppressed? (“Not virally suppressed” means there are high levels of HIV virus in the blood.)
- Can a case manager help HIV-infected MSM and transgender women receive HIV care, take their HIV medicine and achieve viral suppression? (“Viral suppression” means that the HIV virus can no longer be found in the blood.)

What is changing in HPTN 078?

Participants will spend less time in the study. The study follow-up period has been lowered from 24 to 12 months.

Why has this change been made?

The study team has not been able to find enough people to join the study. The team wanted to enroll 356 people. But, after looking for almost two years, we found less than 150 people who could join the study. Thus, we have not been able to answer the first study question.

In addition, without full enrollment, we cannot answer the second study question. But, even without full enrollment, we can still learn important information from the study. For example, how to help people like you stay in HIV care, take your HIV medicine and achieve viral suppression. It will take less time to learn this type of information, which is why follow-up was reduced.

How do these changes affect me?

You will only participate in the study for 12 months.

Your 12-month study visit will be your last study visit. At this visit, you will have your regular study procedures. In addition, you will complete a survey and be tested for syphilis. You will also be asked to take part in an exit interview. You will be paid if you complete the final study visit and exit interview. If you are in the case manager arm of the study, your case manager will help you transition to other support services, if needed, before you leave the study.

If you have already done your 12-month study visit, you will come back for a final study visit. At this visit, you will complete a survey and be tested for syphilis. You will also be asked to take part in an exit interview. You will be paid if you complete the final study visit and exit interview. If you are in the case manager arm of the study, your case manager will help you transition to other support services, if needed, before you leave the study.

Please ask us if you have any questions or concerns. You can reach us at [*sites to insert contact information for study staff*].

The HPTN 078 team thanks you for joining this important study. You are helping us find ways to help people like you stay in HIV care, take your HIV medicine and achieve viral suppression.

Sincerely,

[*Insert name and contact information of Investigator of Record*]

(Participants should initial and date this letter to document receipt.)

Participant Initial

Date