HPTN 078
Enhancing Recruitment, Linkage to Care and Treatment for HIV-Infected Men Who Have Sex with Men (MSM) in the United States

A Study of the HIV Prevention Trials Network (HPTN)

Sponsored by:
Division of AIDS (DAIDS)
United States (US) National Institute of Allergy and Infectious Diseases (NIAID)
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LIST OF ABBREVIATIONS AND ACRONYMS

ACA	Affordable Care Act
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral drug
CAB	Community Advisory Board
CCM	Chronic Care Model
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Continuous Laboratory Improvement Act
CM	Case Manager
CRF	case report form
DAIDS	Division of AIDS
DC-RDS	deep-chain respondent driven sampling
EC	Ethics Committee
HCV	Hepatitis C virus
HHS	(United States Department of) Health and Human Services
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
IoR	Investigator of Record
IRB	Institutional Review Board
LC	(HPTN) Laboratory Center
LDMS	Laboratory Data Management System
LGBT	Lesbian, gay, bisexual, and transgender
LOC	(HPTN) Leadership and Operations Center
MMWR	Morbidity and Mortality Weekly Report
MSM	Men Who Have Sex with Men
NHBS	National HIV Behavioral Surveillance
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
NSFG	National Survey of Family Growth
OHRP	Office for Human Research Protections
PAF	population attributable fraction
PEP	post-exposure prophylaxis
PF	preventable fraction
PrEP	pre-exposure prophylaxis
PRO	(DAIDS) Protocol Registration Office
PSRC	(DAIDS) Prevention Science Review Committee
PUMA	Prevention Umbrella for MSM in the Americas
QA	quality assurance
QC	quality control
RDS	respondent driven sampling
RSC	Regulatory Support Center
SAMISS	Substance Abuse/Mental Illness Symptoms Screener
SDMC	(HPTN) Statistical and Data Management Center

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

SES	socio-economic status
SMC	(HPTN) Study Monitoring Committee
SOC	standard of care
SRC	(HPTN) Scientific Review Committee
SSP	Study Specific Procedures
STI	Sexually Transmitted Infection
UAI	unprotected anal intercourse
VL	viral load

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INVESTIGATOR SIGNATURE PAGE

A Study of the HIV Prevention Trials Network (HPTN)

Sponsored by:
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US National Institutes of Health (NIH)

I, the Investigator of Record (IoR), agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to the Division of AIDS (DAIDS), unless otherwise specified by DAIDS or the HIV Prevention Trials Network (HPTN) Coordinating and Operations Center. Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be made available by the investigators to the HPTN Manuscript Review Committee and DAIDS for review prior to submission.

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

HPTN 078

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

SCHEMA

Purpose: The purpose of this study is to develop and assess the efficacy of an integrated strategy that includes feasible and scalable interventions to identify, recruit, link to care, retain in care, attain, and maintain viral suppression among HIV-infected men who have sex with men (MSM) in the United States (US).

Design: This study will use deep-chain respondent driven sampling (DC-RDS) to identify and recruit HIV-infected MSM who are not virally suppressed. A subset of these men will be enrolled into one of two study arms. The intervention arm will provide a Case Manager (CM) intervention package designed to enhance linkage to care, antiretroviral treatment (ART) initiation, treatment adherence and retention in care. The control arm will provide the standard of care (SOC) for linkage to care, initiation of ART, treatment adherence and retention in care. The primary outcome of the study is viral suppression 24 months after enrollment. Phylogenetic methods will be used to evaluate the relationship between social and sexual networks identified through DC-RDS and viral networks. Mathematical modeling will be performed using demographic, behavioral, and clinical data generated from this study and other sources to estimate the population-level impact of the CM intervention on HIV incidence and to estimate the level of identification, linkage, ART coverage and viral suppression that would be required to achieve a substantial reduction in HIV incidence among MSM in the US settings where the study is conducted.

Intervention: The study intervention [MyLife, MyChoices, MyCare (Step 1), MyCare (Step 2), and MyHealth] is a program designed to enhance linkage, ART initiation, adherence and retention in care for MSM diagnosed with HIV. It will be administered by a trained CM and will include health care and supportive services navigation, adherence counseling, and tailored support for care engagement and treatment adherence.

Population: HIV-infected and HIV-uninfected adolescent ($\geq$ 16 years old) and adult MSM in selected US cities will be screened for this study. Enrollment will be limited to HIV-infected men who are not virally suppressed.

Study Size: Approximately 2700 MSM will be identified and recruited using a DC-RDS strategy in four cities; 356 HIV-infected MSM who are not virally suppressed will be randomized (1:1) to the CM intervention and SOC control study arms of the study.

Study Regimen: There are no specific drug regimens under investigation in this study.

Study Duration: The overall study duration is 48 months: 12 months for DC-RDS recruitment and enrollment; 24 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.

Study Sites: Alabama Vaccine Research Center (Birmingham, AL); Fenway Health (Boston, MA); Johns Hopkins Adult AIDS (Baltimore, MD); and the Ponce de Leon Ctr (Atlanta, GA)

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SCHEMA (Continued)

Primary Objectives:

- Assess the ability of DC-RDS to identify and recruit HIV-infected MSM in the US who are not virally suppressed.
- 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 months after enrollment.

Secondary Objectives:

- Assess HIV prevalence and the proportion of HIV-infected men who are virally suppressed by comparing early wave (approximately 1-6) vs. later (deep) wave (approximately 7-12) DC-RDS participants.
- Compare the proportion of men in the two study arms who are virally suppressed at 3, 6, 9, 12 and 18 months after enrollment.
- 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 two care visits (one in each six month interval, with at least 60 days between these visits) over the 24 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 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 months after enrollment.
- Compare the two study arms with respect to ART adherence at 24 months after enrollment and changes in sexual risk behavior, health care utilization, stigma, substance use and mental health from baseline to 24 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 months.
- Compare the experience of linkage to and ongoing HIV care among participants in the two study arms by conducting and analyzing exit interviews with participants and CMs.

SCHEMA (Continued)

Exploratory Objectives:

- Use phylogenetic methods to evaluate the relationship between HIV strains in men identified via DC-RDS. Men who were recently infected at screening will be identified using a multi-assay algorithm. If viral networks are identified (e.g., clusters, linked infections), compare these networks to social and sexual networks, and evaluate the relationship of behavioral, socio-demographic, clinical, and virologic characteristics to viral networks.

- Use laboratory assessments to characterize the study cohort and to evaluate the impacts of study interventions. These assessments may include analysis of HIV drug resistance and antiretroviral (ARV) drug use. Additional analyses may be conducted to analyze HCV strains, including phylogenetic analysis of HCV. Samples from this study may also be used to evaluate the performance of assays related to HIV and HCV infection.

Modeling Objective:

- Develop, calibrate, and use a mathematical model of HIV transmission among MSM in the US to assess the short and long-term population-level impact of the study strategy, and its independent CM intervention components (e.g., HIV testing, ART uptake, retention in care and viral suppression), on HIV incidence and to estimate the level of viral suppression required to reduce HIV incidence in the MSM community by 10%, 20%, 30%, and 50% over 2, 5 and 10 years, and the likelihood of and time to elimination.

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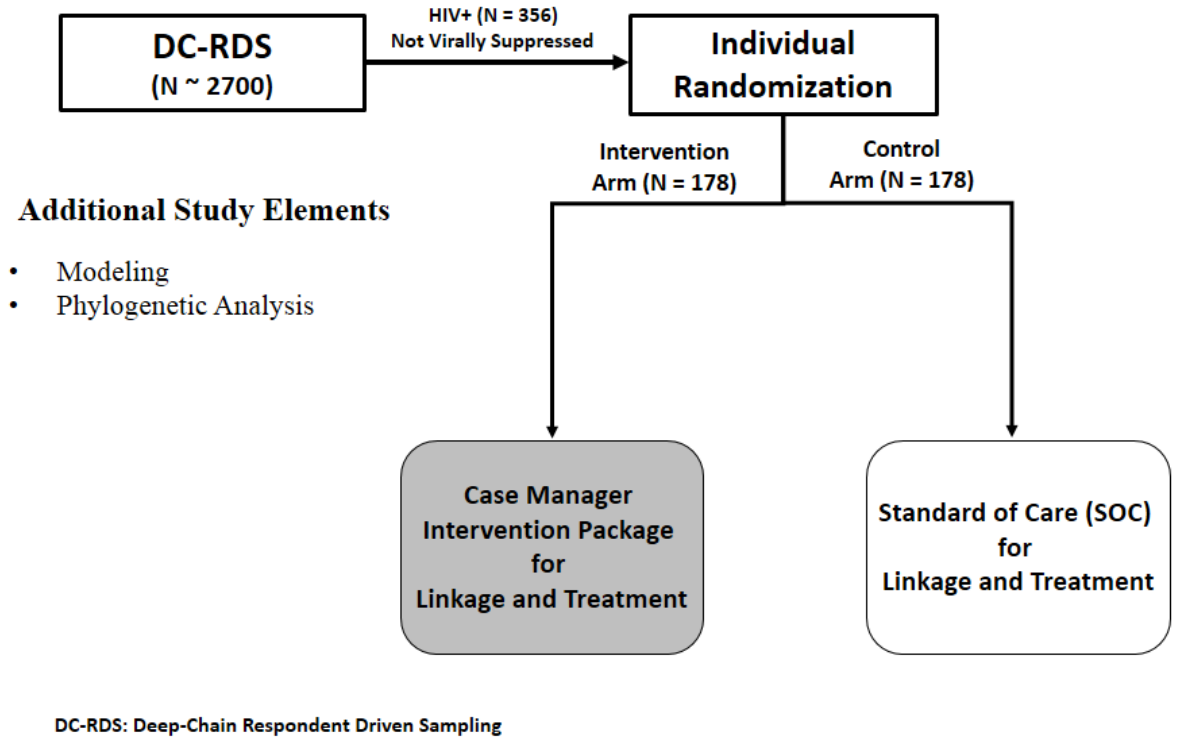
OVERVIEW OF STUDY DESIGN



DC-RDS: Deep-Chain Respondent Driven Sampling

1.0 INTRODUCTION

1.1 Background and Prior Research

The United States (US) is currently undergoing a widespread and severe HIV epidemic among gay, bisexual, and other men who have sex with men (MSM), which has been underway since at least 2003.[1] In their most recent report, the US Centers for Disease Control and Prevention (CDC) reported that 62% of all new infections in the US were among MSM, a group who represent at most 2-4% of US adult men, and 1-2% of all adults.[2] The US epidemic is strikingly concentrated in MSM populations—the only group among whom HIV infections burdens were rising in 2011. This epidemic is characterized by marked racial and ethnic disparities, with the highest HIV burdens among Black MSM, followed by Latino MSM.[3] The US MSM epidemic is marked by much higher incidence densities among the youngest MSM, those aged 13-24.[4] HPTN 061, an incidence study in Black MSM, found a 3% incidence rate overall in this population, with a 5.9% incidence rate in those 18 to 29 years old.[5] There is also a marked geographic component to the US epidemic among MSM, with the highest rates of incident HIV infection in both Black and White MSM found in the South. These health disparities are not limited to HIV prevalence and incidence burdens, but rather are also seen in lower rates of regular HIV testing, in lack of awareness of HIV status, in late presentation for HIV care, in poor adherence to antiretroviral therapy (ART), and in the failure to achieve viral suppression.[3]

The continuum of care, or cascade of care, has been useful to help characterize HIV burdens and understand gaps in HIV responses. The CDC estimate for the US population as a whole is that of the 1.2 million estimated persons living with HIV infection, 1 in 7 do not know they are living with HIV, only 4 in 10 are in care, and only 3 in 10 have sustained viral suppression.[6] African American MSM do less well across each step of this continuum, with an overall outcome of being half as likely to be fully virally suppressed if living with HIV infection compared to men of all other racial/ethnic categories.[3] To address these health disparities, and to improve responses for gay and other MSM it is critical to reach higher proportions of HIV-infected MSM who are not virally suppressed, enhance their linkage to care, and increase the proportion of these men who can achieve, and maintain, HIV suppression. Intervention strategies and packages that can achieve these goals must be acceptable, feasible and scalable. This study will attempt to address two critical steps in the continuum of care for MSM in the US: enhanced outreach and recruitment of MSM living with HIV infection but not virally suppressed through deep-chain respondent driven sampling (DC-RDS); and enhanced treatment and care to increase the proportion of MSM who achieve sustained viral suppression through a case management (CM) intervention.

1.1.1 The Need to Enhance Recruitment

The US CDC estimates that 14% of Americans living with HIV infection remain undiagnosed and unaware of their HIV infection status.[6] An additional 60% of those living with HIV are not currently in HIV care[6]—meaning that almost 70% of persons in the US with HIV infection are not currently on treatment or virally suppressed. This is a challenge for the health of these individuals, but also represents a pool of untreated HIV infections that drive ongoing transmission. Despite active testing and outreach campaigns in many jurisdictions, uptake of HIV testing remains too low in many communities, including among MSM, and is particularly challenging in minority communities and among younger age groups of MSM. Black MSM are nearly 5 fold less likely to have had a recent HIV test compared to White MSM in the US.[3] Active recruitment, and the use of innovative techniques for recruitment, is an urgent HIV research priority for controlling HIV infection among MSM.

Respondent driven sampling (RDS) has demonstrated effectiveness in reaching hard to sample populations, including among minority and low socio-economic status (SES) MSM in the US. Long Chain RDS, where referral chains are maintained over long waves of recruitment, is an innovative approach that has the potential to reach more hidden, marginalized and HIV-untested, unlinked, and not virally suppressed MSM living with HIV infection.

1.1.2 Deep-Chain Respondent Driven Sampling (DC-RDS)

RDS relies on the identification and enumeration of a discrete number of "seeds" who are incentivized to refer members of their social or sexual networks, who then repeat the process, generating successive waves of recruitment. RDS has been used successfully in the US and abroad to recruit marginalized MSM. RDS studies have reported success in recruiting MSM who have very low incomes, are homeless, men engaged in sex work, non-gay-identified and/or bisexually active men.[7, 8] Moreover, studies that have used RDS to recruit black MSM in the US consistently find substantial proportions of HIV infected but untreated MSM in each respective study.[8-10] These studies obtained fairly similar samples despite varying demographics and risk profiles among initial seeds across the studies. This suggests that RDS can be a useful recruitment tool for research on marginalized populations and a method that has demonstrated considerable success in doing so in the US context, which is the focus of the proposed HPTN 078 study.

DC-RDS, also referred to as long chain RDS, where recruitment chains continue to propagate beyond the standard sixth wave of recruitment, has shown the potential to reach the most marginalized subsets of study participants, hence our interest in using this approach as a recruitment tool.[11, 12] A novel secondary aim of the study will be to compare early (approximately wave 1-6) versus later (approximately wave 7-12) recruitment waves to assess the ability of DC-RDS to identify HIV-infected MSM who are not virally suppressed in the selected cities.

1.1.3 Evidence for Effectiveness of Early ART

There is strong biological plausibility that effective early ART can reduce sexual transmission of HIV between MSM by decreasing HIV viral load and, hence, infectiousness. Ecological evidence from San Francisco suggests that early ART initiation and high levels of treatment coverage may be associated with decreases in new HIV infections among MSM at population levels.[13] However, the ecological and other epidemiologic data are mixed, and recent reports from the United Kingdom and from France suggest rising rates of HIV infection in MSM despite high ART coverage of HIV-infected men in care.[14, 15]

In HPTN 052[16], early ART initiation was confirmed to have high efficacy in preventing transmission among HIV serodiscordant couples. However, only 37 male-male discordant couples were recruited into HPTN 052 – with only one male-male couple in the US. Furthermore, recent epidemiologic and modeling data suggest that, in many populations of MSM, primary partnerships account for only a minority (30-35% in the PUMA [Prevention Umbrella for MSM in the Americas] modeling estimates) of HIV transmissions, with the majority occurring between non-primary sexual partners.[17] Thus, the population-level effectiveness of ART as HIV prevention among MSM is unknown and may not be measured most effectively through approaches based on discordant couples. Enhanced treatment of HIV-infected men within networks and at community levels may be important in reducing the spread of the epidemic among MSM.

1.1.4 Engagement in Care among MSM in the US

As there is a dearth of research on engagement-in-care strategies specific to the MSM population, challenges remain particularly prevalent among minority MSM in the US. Health care system navigation may offer a promising engagement-in-care strategy for MSM.[18] Among young MSM of color there is a particular need for strengthened and tailored strategies for retention in care with links to social supportive services due to the multiple challenges in this group (e.g., access to health care, poverty, unemployment, stigma).[19-21]

1.1.5 Interventions to Optimize Retention and Adherence

It is established that a combination of components and strategies best addresses challenges to HIV treatment and care; thus, the intervention package for linkage, retention and treatment adherence, with case management at its core, will draw from several evidence-based interventions.[22-25] The Care Coordination Model as outlined by Craig et al in 2011[26] has been shown to optimize linkage to and retention in care.[27-29] With the advent of the Affordable Care Act (ACA), care coordination must include negotiating affordable care options available to study participants.

Behavioral interventions with the strongest beneficial impact on treatment adherence are cognitive-behavioral counseling interventions with a primary focus on treatment adherence.[30-32] In these sessions, patients are provided with tailored counseling to focus on problem solving and communication to address risk reduction, HIV disclosure, social support for adherence, and barriers to ART adherence.[32-34]

Use of mobile technology to provide supportive reminders for medication adherence has also been shown to be effective in enhancing retention and adherence.[35-37] Specifically, a tailored text-messaging strategy has recently shown promise with MSM.[38]

1.2 Rationale

The purpose of this study is to develop and assess the efficacy of an integrated strategy that includes feasible and scalable interventions to identify, recruit, link to care, retain in care, and attain viral suppression among HIV-infected MSM in the US. This research is important since MSM are the most disproportionately affected population for HIV in the US, and there is an urgent need to develop innovative strategies to address this health disparity across the continuum of care. Sex between men accounted for an estimated 62% of newly identified HIV infections in the US in 2012, according to the US CDC, making enhancement of the effectiveness of engagement in care and treatment for MSM of primary importance for controlling the US domestic HIV epidemic. This study is focused on US urban MSM living with HIV infection who are not successfully virally suppressed. All MSM identified as HIV-infected and not virally suppressed will be offered linkage to care and immediate ART—an option not available in many other settings with severe epidemics among MSM. Since current HPTN sites, and concentrations of MSM in the US are primarily urban, this study will focus on urban MSM populations but may yield insights of relevance to improving outcomes for sub-urban and rural MSM in the US.

The recruitment component of this study will help refine the designs of future research and program efforts to enhance outreach, increase testing uptake and increase linkage for HIV-infected MSM who are not virally suppressed. This population includes all MSM with non-suppressed HIV viral loads, including men who are HIV-infected and not previously diagnosed, men who are aware of their HIV infection but not currently linked to care, and men who may have been in care, or are currently in care, but are not successfully virally suppressed.

Men in all of these groups who meet enrollment criteria will be offered enrollment in the enhanced case management intervention for linkage, retention, treatment initiation and medication adherence. DC-RDS will be assessed for its efficacy in reaching more hidden, marginalized, previously undiagnosed, and HIV-infected and not virally suppressed MSM. Future trials of enhanced treatment interventions, and of Treatment as Prevention (TasP) at community levels among MSM, will depend on the ability to reach these challenging subsets of MSM and to link them to care and treatment.

Despite clear evidence of treatment as prevention and the impact of ART on the quality and quantity of life, current data on success across the HIV treatment cascade demonstrates a need to improve both access to care and treatment adherence. Interventions to ensure MSM living with HIV and not virally suppressed are linked to and remain in care to achieve virologic control are limited and have had mixed results.[39, 40] Case management models, in which skilled providers facilitate HIV treatment plans to ensure appropriate and timely care are given, have been shown to be safe and improve treatment outcomes.[41-43] Presently, these interventions are limited to key affected populations and there is little evidence to describe the specific aspects of a case management model for linkage to care. Many studies utilizing case management models have demonstrated substantial improvements in disease outcomes, including HIV.

The Chronic Care Model (CCM) identifies essential elements of a health care system that encourage high-quality chronic disease care in a bundled approach.[41, 44-46] These elements provide the conceptual framework for the CM intervention, which is an approach to improve linkage, retention and controlled viremia in HIV-infected MSM. Tailoring of a culturally-sound case management model for MSM living with HIV and not virally suppressed may improve linkage, access, and retention in care and ultimately result in better sustained virologic control.

The use of modeling is critical to assess the potential impact of increases in the proportion of HIV-infected MSM who are successfully virally suppressed on HIV incidence in MSM networks and communities. Since this study will have an endpoint of viral suppression among HIV-infected MSM, modeling will be used to estimate the potential impact of the proposed CM intervention strategy, should it be successful, on ongoing sexual HIV transmission in selected urban US MSM networks. This ongoing MSM transmission, despite current efforts across the US, remains the largest component of incident HIV infections in the country.

Phylogenetic and phylodynamic assessment of HIV infections among MSM could add important insights to the outreach and recruitment aims of this study. Since DC-RDS is a chain referral approach that is dependent on social and sexual networks, and participants recruit their network members for iterative recruitment waves, DC-RDS allows for the construction of network chains of referral and relatedness. As recruitment waves propagate beyond initial seeds, recruitment goes further into populations, eventually reaching significant proportions of populations with shared characteristics and who are connected through social networks. The ability to assess linkages at viral levels within these networks may provide critical insights into HIV transmission dynamics in urban MSM communities.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

The primary objectives of the study are to:

- Assess the ability of DC-RDS to identify and recruit HIV-infected MSM in the US who are not virally suppressed.
- 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 months after enrollment.

2.2 Secondary Objectives

The secondary objectives of the study are to:

- Assess HIV prevalence and the proportion of HIV-infected men who are virally suppressed by comparing early wave (approximately 1-6) vs. later (deep) wave (approximately 7-12) DC-RDS participants.
- 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.
- 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 two care visits (one in the each six month interval, with at least 60 days between these visits) over the 24 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 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 months after enrollment.
- Compare the two study arms with respect to ART adherence at 24 months after enrollment and changes in sexual risk behavior, health care utilization, stigma, substance use and mental health from baseline to24 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 months.
- Compare the experience of linkage to and ongoing HIV care among participants in the two study arms by conducting and analyzing exit interviews with participants and CMs.

2.3 Exploratory Objectives

The exploratory objectives of the study are to:

- Use phylogenetic methods to evaluate the relationship between HIV strains in men identified via DC-RDS. Men who were recently infected at screening will be identified using a multi-assay algorithm. If viral networks are identified (e.g., clusters, linked infections), compare

these networks to social and sexual networks, and evaluate the relationship of behavioral, socio-demographic, clinical, and virologic characteristics to viral networks.

- Use laboratory assessments to characterize the study cohort and to evaluate the impacts of study interventions. These assessments may include analysis of HIV drug resistance and antiretroviral (ARV) drug use. Additional analyses may be conducted to analyze HCV strains, including phylogenetic analysis of HCV. Samples from this study may also be used to evaluate the performance of assays related to HIV and HCV infection.

2.4 Modeling Objective

The modeling objective of the study is to:

- Develop, calibrate, and use a mathematical model of HIV transmission among MSM in the US to assess the short and long-term population-level impact of the study strategy, and its independent CM intervention components (e.g., HIV testing, ART uptake, retention in care and viral suppression), on HIV incidence and to estimate the level of viral suppression required to reduce HIV incidence in the MSM community by 10%, 20%, 30%, and 50% over 2, 5 and 10 years, and the likelihood of and time to elimination.

2.5 Study Design

The overall design of this study reflects the primary goal, which is to develop and assess an integrated scalable strategy to identify, recruit, link to care, retain in care, and achieve HIV viral suppression among urban US MSM who are HIV-infected and not successfully virally suppressed. To outreach, identify and recruit HIV-infected MSM who are not virally suppressed, DC-RDS will be implemented in four US cities (Atlanta, GA; Baltimore, MD; Birmingham, AL; and Boston, MA). Participating cities will have HPTN sites with evidence of high HIV burdens among MSM and interest in participating in the study. DC-RDS has been shown to be effective in reaching and identifying hard to reach subsets of MSM, including low SES, non-gay identified, and ethnic and racial minority MSM who are less likely be in HIV care and to be virally suppressed. The primary outcome of the recruitment component of the study is to assess the ability of DC-RDS to identify and recruit HIV-infected MSM in the US who are not virally suppressed.

MSM recruited through DC-RDS who meet enrollment criteria will be randomized (1:1) to one of two study arms. The intervention arm will provide a Case Manager (CM) intervention package designed to enhance linkage to care, antiretroviral treatment (ART) initiation, treatment adherence and retention in care using a case management-based intervention. The SOC control arm will provide the standard of care (SOC) for linkage to care, initiation of ART, treatment adherence and retention in care. The primary outcome of the CM intervention phase is viral suppression 24 months after enrollment.

Phylogenetic methods will be used to evaluate the relationship between social and sexual networks identified through DC-RDS and viral networks. Mathematical modeling will be performed using demographic, behavioral, and clinical data generated from this study and other sources to estimate the population-level impact of the CM intervention on HIV incidence and to estimate the level of identification, linkage, ART coverage and viral suppression that would be required to achieve a substantial reduction in HIV incidence among MSM in the US settings where the study is conducted.

3.0 STUDY POPULATION

Approximately 2700 sexually active MSM (~675 in each participating city) will be recruited for HIV testing via DC-RDS. 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.

3.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible for inclusion in the study (screening, CM intervention arm and SOC control arm):

- Biological male (currently and at birth)
- Self-report of history of anal intercourse with another man within the last 6 months
- 16 years or older (At sites with IRB approval, MSM age 16-17 years old can be recruited and enrolled if they are willing and able to provide written assent, and if a parent or legal guardian is willing and able to provide written informed consent.)

In addition to the criteria above, individuals who meet all of the following criteria are eligible for enrollment into the CM intervention and SOC control arms:

- HIV-infected, as defined in the HPTN 078 Study-Specific Procedures (SSP) Manual
- Not virally suppressed (defined as HIV VL > 1000 copies/ml, note that this VL cut-off is being used as an indicator of adherence or resistance issues for study inclusion only)
- Can receive care at one of the participating clinics (listed in the HPTN 078 SSP Manual)
- No current plan to relocate in the 24 months following enrollment

3.2 Exclusion Criteria

Individuals who meet any of the following criteria will be excluded from the study (screening, CM intervention arm and SOC control arm):

- Unable or unwilling to provide consent (or assent for a minor with parent or legal guardian consent) for study participation
- Transgender women
- Active or previous participation in an HIV vaccine trial, unless evidence can be provided documenting randomization to the placebo arm.
- Any condition that, in the opinion of the Investigator of Record (IoR), would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

In addition to the criteria above, individuals who meet any of the following criteria are excluded from enrollment into the CM intervention and SOC control arms:

- Current participation in a linkage or ART adherence study

3.3 Recruitment Process

DC-RDS will be used to recruit MSM into this study. In this method, 8-10 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.

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.

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.

3.4 Co-Enrollment Guidelines

Participants will not be eligible for study participation (screening or enrollment) if they are actively or have ever been enrolled in an HIV vaccine trial, since this may affect the anti-HIV antibody profile, complicating cross-sectional HIV incidence estimation and identification of participants who were recently infected at the time of screening. Participants will not be eligible for enrollment into the CM intervention and SOC control arms if they are currently participating in a linkage or ART adherence study. Once randomized, participants cannot be co-enrolled into other linkage or ART adherence studies.

3.5 Participant Retention

Locator information will be collected from each participant, so that he can be found if his phone number or address changes. Each site will be asked to create a retention plan to maximize the level of participation in study-required visits (follow-up visits and the final visit); however, sites will use their standard-of-care for retaining participants in clinical care throughout the study. The HPTN 078 SSP Manual will outline procedures for participants who wish to change clinics.

3.6 Participant Withdrawal and Early Termination

Participants may voluntarily withdraw from the study for any reason at any time. Site IoRs may, with the approval of the Protocol Chair and the Protocol statistician, withdraw participants before their scheduled termination visit to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities or site Institutional Review Boards (IRBs) terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation (M24 visit procedures) of participants who terminate from the study prior to Month 24, and study staff will record the reason(s) for all withdrawals in participants' study records.

3.7 Study Sites

Participants may be followed at participating HIV clinics in each of the four cities. All participating clinics must be able to provide the current SOC for HIV-infected MSM and be willing to provide participant information to the study team for analysis. In addition, a survey documenting standard-of-care practices will be completed for each clinic that cares for HIV-infected MSM enrolled in the study.

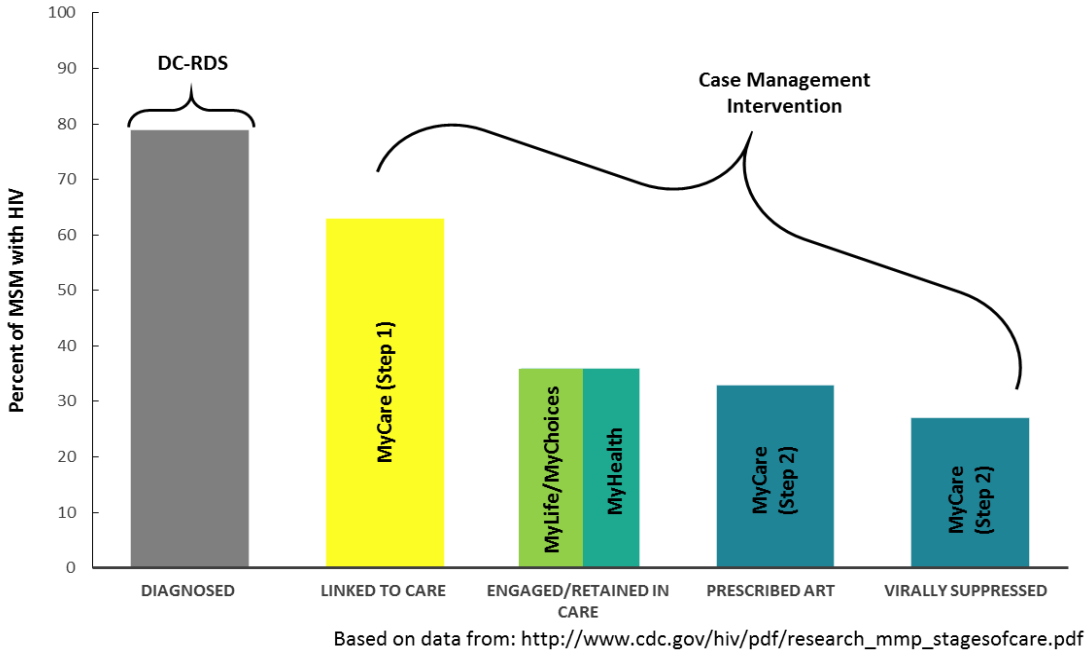
4.0 STUDY INTERVENTION

The study CM intervention [MyLife, MyChoices, MyCare (Step 1), MyCare (Step 2), and MyHealth] is a program designed to enhance linkage, ART initiation, adherence and retention in care for MSM diagnosed with HIV. It will be administered by a trained CM and will include health care and supportive services navigation, adherence counseling, and tailored support for care engagement and treatment adherence. Table 1 and Figure 1 summarize each component, the element of the HIV care cascade it addresses and the evidence behind the CM intervention; a more complete table is included in Appendix V.

Table 1: Tailored Case Management (CM) Intervention Components in At Risk US Populations (2005 – 2015)

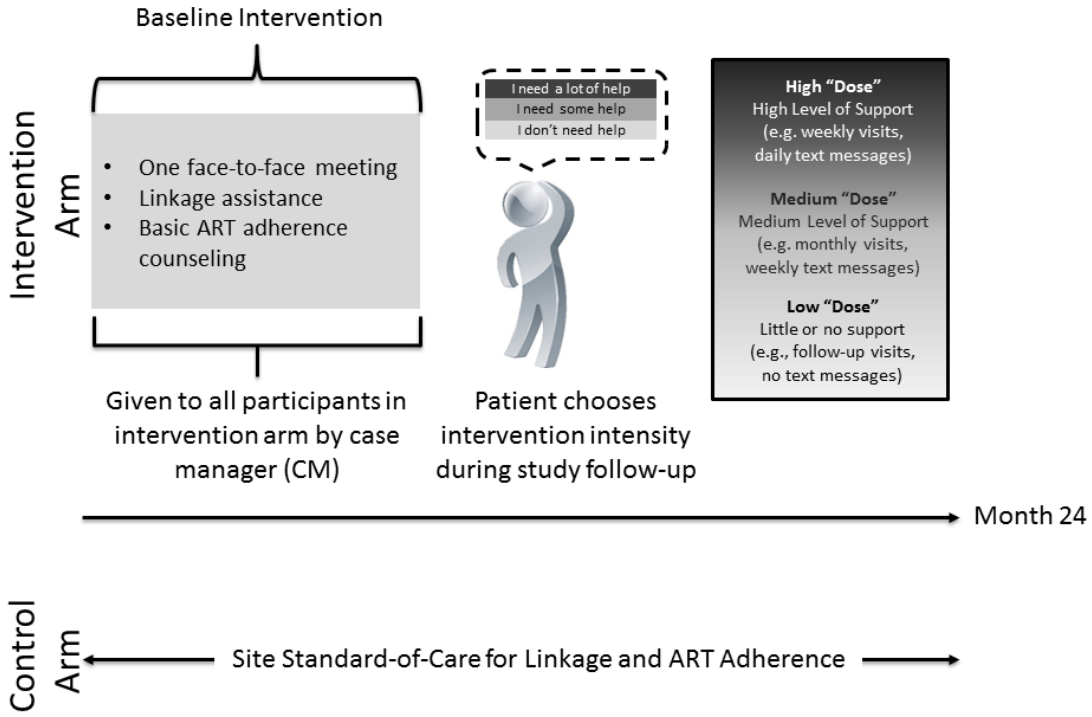
HPTN 078 Intervention Component	Cascade Component	Citations
MyLife	- Linkage to care - Engagement in care - Retention in care - Self-management - Viral suppression - Inter-personal relationship building - Durability	Hightow; 2011[48] Quinlivan; 2013[49] Rajabiun; 2007[50] Yehia; 2015[51]
MyChoices	- Linkage to care - Engagement in care - Retention in care	Christopoulos; 2013[52] Craw; 2010[53]
MyCare (Step 1)	- Linkage to care - Engagement in care - Retention in care - Viral suppression - Durability	Bradford; 2007[27] Willis; 2013[47]
MyCare (Step 2)	- Engagement in care - Retention in care - Adherence - Viral suppression - Inter-personal relationship building - Durability	Hayley; 2014[58] Holtzman; 2015[59] Naar-King; 2009[60] Nelsen; 2013[61] Remien; 2005[62] Simoni; 2006[32]
MyHealth	- Linkage to care - Engagement in care - Retention in care - Adherence - Self-management - Inter-personal relationship building - Viral suppression - Durability	Gilman; 2012[54] Hightow; 2011[55] Lewis; 2013[38] Maulsby; 2015[56] Schnall; 2015[57]

Figure 1: Relationship between the HIV Care Cascade and the CM Intervention



The CM will help each participant enrolled into the CM intervention arm to link to HIV care, initiate ART, remain adherent to medication and keeping clinical appointments. Each CM will have prior case management experience and will be trained to carry out the specified intervention aimed at improving disease management and reducing HIV viral load for patients with HIV. The CM-to-participant ratio will be approximately 1:42 over the 24-month period. As shown in Figure 2, the frequency, content and type (in person, email, phone, text message) of interactions will be driven by each patient's desire and need for support, but will minimally follow the schedule of events (see Appendix I). All CM-participant interactions will be documented (frequency and duration) to assess the feasibility and scalability of the CM intervention. To ensure uniformity and fidelity of the intervention across sites, each CM will undergo a standardized, comprehensive training program, and each mandatory session (at required study visits) will be audio recorded and a small percentage will be assessed against a standard counselling index, as described in the HPTN 078 SSP Manual.

Figure 2: Overview of CM-Administered Study Intervention



Note: Some participants may choose to meet in person with the CM on a very frequent basis (e.g. weekly); these visit will be recorded, however, such visits are not mandatory and there are no required study procedures during them.

This CM-led model builds upon the existing CDC-endorsed Comprehensive Risk Counseling and Services for Persons with HIV[63], which focuses on the prevention of HIV transmission. The model combines aspect of clinical care coordination to include; a) recruitment and engagement (MyLife); b) inventory of available resources (MyChoices); c) patient navigation to clinical care (MyCare (Step 1)); d) adherence counseling (MyCare (Step 2); e) retention and follow-up (MyHealth).

The approach of the CM follows an approach similar to HPTN 073 in the use of a self-determination theoretical approach, which hypothesizes that reestablishing autonomy is a key element for long-term engagement in care for some patients.[49] Additionally, the Gelberg-Andersen Behavioral Model for vulnerable populations[64] will be used to identify enabling, predisposing and need variables that impact adherence and retention in care, which has been effectively demonstrated in women living with HIV, but not in an MSM group.[65] The role of the CM within each of the five components is described below.

Participants enrolled into the SOC control arm will be provided with the existing programs for referral to HIV treatment and support services without additional CM coordination.

4.1 Linkage to Care and ART Initiation (MyLife, MyChoices, MyCare (Step 1))

4.1.1 Engagement (MyLife)

The MyLife component is the first step of the CM intervention as developing a therapeutic or interpersonal relationship with the participant is the paramount first step. Engaging with the participant is an effective strategy that has been shown to improve retention.[58] Part of this engagement process is to attempt to understand the participant's state of mind after the HIV diagnosis and address any HIV-related questions he may have. It may become necessary to end the first session here depending on the individuals needs related to their diagnosis. This session will include an HIV counseling intervention about the new diagnosis and an overview of the case management model in support of the patient. The CM will be taught motivational interviewing skills to facilitate participant engagement into clinical practice.

After the initial question-answer period, the CM will seek to understand the predisposing, enabling and health needs of the participant.[64] A standardized instrument will be utilized to elicit this information from the patient. Once these data are available, the CM will discuss and assist the participant to develop an individually-tailored plan that is designed utilizing self-determination theory. Self-determination theory is anchored by three core components: (1) autonomy support-provision of evidence-based health guidance and supporting the participant-endorsement of the plan they believe best meets their needs and fits within their life circumstance; (2) competence support-expression of belief in the participant's ability to implement his self-endorsed plan and provision of guidance for acquiring the necessary skills and resources for successful implementation; and (3) relational support-expression/demonstration of genuine care and concern for the participant's successful implementation of the plan (e.g., follow-up phone/text check-ins). These three components are theorized to facilitate the adoption and maintenance of health behaviors. A comprehensive training program on the use of this model will be provided to all CMs.

4.1.2 Inventory of Available Resources (MyChoices)

MyChoices will involve a discussion of resources available to meet the participants stated healthcare needs. The CM will have a comprehensive listing of available HIV, substance abuse, mental health, and other available resources to discuss with the participant. The CM will provide guidance on options that work within the delineated plan and make modifications based on the participant's needs and review of the available resources.

4.1.3 Patient Navigation to Clinical Care (MyCare (Step 1))

MyCare (Step 1) supports the decision to initiate HIV care and will include motivational interviewing activities to coach the client toward seeking and initiating care. Once care decisions have been made by the participant, the CM will offer to facilitate entry into the care facility selected by the patient. This will include the establishment of necessary appointments, facilitation of paperwork and registration materials, pre-clinical laboratory evaluations, evaluation of provider options within the clinical site as well as introductions of the clinical team through either website review, phone calls, or a clinic visit with onsite team prior to the first visit. All participants will be encouraged to initiate (or re-initiate) ART in consultation with their healthcare provider.

4.2 Adherence Counseling (MyCare (Step 2))

In conjunction with ART initiation, the CM will deliver the evidence-based adherence counseling intervention, which will be modeled after Life Steps[31], a single-session intervention that is grounded in cognitive-behavioral principles that are at the core of several successful ART adherence interventions.[25, 32, 62, 66] The adherence counseling session will address basic psycho--education about HIV and ART, planning and problem-solving for accessing and maintaining a steady supply of medication, formulation of a daily medication schedule, cues for pill-taking, coping with side effects and/or other patient concerns, developing a plan to mitigate side effects, and responses to slips in adherence. This counseling will be provided face-to-face prior to, at the time of, or in the very early stage of ART initiation. Participants will be encouraged to bring a support partner to the adherence counseling sessions, if they so desire, which has been shown to be effective for long-term medication adherence.[62, 66, 67] The counseling intervention allows for tailoring to the participants specific needs, as well as additional counseling sessions, if needed. MyCare (Step 2) adds to this evidence-based approach by recognizing that adherence to treatment is a personal choice that is grounded in a variety of behavioral and psychosocial domains. Intention to adhere to treatment will be added as part of the MyCare (Step 2) component.[61]

4.3 Communication, Retention and Follow-up (MyHealth)

MyHealth is based on the premise that a patient engaged in self-management and supportive strategies will feel more empowered to take ownership of his own healthcare needs. In addition, there is accumulated evidence for the acceptability and preference for two-way text messaging for adherence support among diverse populations, including MSM.[35-38] As such, tailored communication support will be offered to facilitate ongoing adherence. The CM will work with each participant to determine his desire for supportive adherence reminders, his preferred method of communication (text message, email or phone call), and the frequency and schedule for these messages. In this way, the participant is being empowered to take the lead with recommendations and guidance from the CM. This type of messaging is interactive in that it allows for a response from participants, in case a participant needs additional information or assistance. The frequency and content of these communications may change over the course of the intervention, depending on the needs of the participant.

5.0 STUDY PROCEDURES

An overview of the study visits and procedures is presented in Appendix I. Additional information is provided below on visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites will be provided in the SSP Manual.

5.1 Screening Visits (S1, S2)

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. 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) (a maximum of 14 days after S1) 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. 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).

5.1.3 Procedures for Participants Who are Determined to be HIV-Uninfected

Participants who are determined to be HIV-uninfected (see HPTN 078 SSP Manual) will be given information on HIV prevention, including current information about pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). These participants are not eligible for enrollment into the CM intervention or SOC control arms.

5.1.4 Procedures for Participants Who are Confirmed to be HIV-Infected

Participants who are confirmed to be HIV-infected (see HPTN 078 SSP Manual) will be screened for participation in the intervention, and, if eligible, will be invited to be enrolled into the CM intervention or SOC control arms. If an individual is eligible for randomization, but chooses not to participate further in the study, he will be referred to local HIV care facilities.

5.1.5 Procedures for Participants Whose HIV Status is Inconclusive

Participants whose HIV status is not clear after the second screening visit will be referred to a local care provider for further evaluation and follow-up. If the person is later confirmed to be HIV-infected, and is eligible, he may be enrolled into the study.

5.2 Enrollment Visit (M0)

During this visit (a maximum of 14 days after S2), participants will be consented for enrollment and randomized to either the CM intervention or SOC control arm. Participants will be asked to sign a release of medical information, locator information will be confirmed and they will be asked to complete a questionnaire (see Appendix II). All participants will be offered HIV testing for their partners. Depending on the results of the partners' HIV test results, partners will be referred to appropriate HIV care services or other HIV-related studies. [*Note: partner testing will be done outside of the study and results will not be recorded.]* In addition, the intervention will begin at this visit for those randomized to the CM intervention arm, and, if appropriate, ART may be initiated at this visit. (Note that ART is not provided by the study, nor prescribed by the CM.)

5.3 Tailored Communication

Once an individual is enrolled into the CM intervention arm, he will decide how much, if any, text message, email or phone reminders he would like to receive to support ART adherence. These reminders will be tailored to the needs of the participant so that they are effective, while maintaining privacy. The CM will facilitate the distribution of these messages and respond to requests for assistance via these two-way modes of communication. This tailored communication to support ART adherence will not be offered to participants in the SOC control arm.

5.4 Monthly Contact

The CM will contact each participant randomized to the CM intervention arm on a monthly basis to confirm his locator information, to check-in with the participant regarding HIV and ART management, and to collect any social impacts due to study participation. Participants may choose this contact to be in person or by text message, email or phone call. No monthly contact will be made with participants in the SOC control arm.

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

Follow-up Visits will take place at Months 3, 6, 9, 12 and 18 for all participants (CM intervention and SOC control arms). During this face-to-face visit, locator information will be confirmed, social impacts will be collected, partner HIV testing will be offered, HIV viral load and CD4 cell count testing will be conducted, and plasma will be stored. For those randomized to the CM intervention arm, the intervention will be implemented by the CM.

5.6 Final Visit (M24)

The Final Visit will take place at Month 24. This visit will be identical to a Follow-up Visit, except that blood will be collected for syphilis testing and questionnaires will be administered (see Appendix I). An exit interview will also be conducted with all participants. If the syphilis test is positive, participants will be asked to return for an ad hoc visit to receive the results and be referred for care.

5.7 Data Collection on ART Initiation and Visit Attendance

Information about ART initiation (date, CD4 cell count and HIV viral load) (if it takes place during study follow-up) and overall visit attendance will be collected from all participants' medical records.

5.8 Questionnaires

5.8.1 Participant Questionnaires

Questionnaires in the following domains will be administered over the course of the study: demographic; PrEP/PEP/ART use history; HIV testing history; sexual matrix module/sexual risk behavior; health care utilization; engagement in the lesbian, gay, bisexual and transgender (LGBT) community; post recruitment questions; medication adherence; stigma; substance abuse; and mental health. The schedule for these questionnaires is provided in Appendix II. When possible, the domain questionnaires will be adapted from recent MSM-focused HPTN studies such as HPTN 061 and 073 to allow cross comparison. Additionally, validated questions/scales from the literature will be used to gain information in domains that are vital to understanding the impact of the study design and intervention. Information on the focus of each domain is provided below:

- **Demographic:** Data collected in this domain will include information such as age, gender, marital status, education, annual income, race/ethnicity and health insurance status.

- **PEP/PrEP/ART:** Information collected in this domain will focus on actual behaviors and use of PEP/PrEP/ART in the last 12 months. Daily and intermittent use of PrEP in the community will also be evaluated.

- **HIV testing history:** The HIV testing history domain will document how many times the participant has been tested for HIV in the past year and the month and year of the most recent HIV test. In addition, this domain will document whether or not the participant received the results and if so, the result of the test.

- **Sexual matrix module/Sexual risk behavior:** Information collected within these domains will include information on number of partners, frequency and types of sexual acts, and geography of the sexual experiences. This information will help identify sexual exposures inside and outside the defined community. The questions in this domain will be adapted from both HPTN 061 and HPTN 073 as well as the Berry sexual activity matrix.[68, 69]

- **Health care utilization:** Information collected in this domain will include information on health care utilization and services and assess engagement at baseline. Trust between the clinician and patient will also be evaluated. Information in this domain will also be collected

at the final visit to assess any supplemental services that have been accessed outside the study.

- **Engagement in the LGBT community:** Information collected in this domain will include information on how well people are engaged and connected in the LGBT community. This domain will supplement the post recruitment questions and allow the team to evaluate the effectiveness of DC-RDS in finding those connected and individuals that are hidden in the community. This may reveal any association with the likelihood of being undiagnosed.

- **Post recruitment questions:** Information collected in this domain will focus on evaluating the effectiveness of DC-RDS and recruitment strategies by participants.[70, 71]

- **Stigma:** Information collected in this domain will be very focused on self-stigma (internalized homo-negativity) and HIV stigma (with consideration of impact on HIV testing and adherence). This questionnaire domain is being adapted from Herek et al 1997.[72]

- **Substance abuse and mental health:** Information collected in this section will focus on depression, post-traumatic stress disorder, anxiety and substance abuse. These assessments will be brief screeners that the case manager can use to intervene or provide referrals. The Substance Abuse/Mental Illness Symptoms Screener (SAMISS)[73, 74] will be the primary source for this domain.

- **Medication adherence:** This domain will be self-reported medication adherence. A three-item scale developed by Wilson et al,[75] which has recently been shown to be correlated with HIV viral load outcomes across different populations, will be used.

- **Exit Interview:** A questionnaire and a semi-structured qualitative interview will be administered to participants asking them to describe their experiences with linkage-to-care, adherence and the CM intervention; information will be collected from both arms about outside interventions/care. Such exit interviews will also be conducted with the CMs, with the questions tailored for their role in the study.

5.8.2 Site Questionnaires

Site questionnaires will administered to each site providing care to HPTN 078 enrolled participants in order to document the standard of care. These surveys will be administered annually to capture sites' normal procedures throughout the duration of the study.

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

As this study only involves low-risk activities (recruitment activities; testing for HIV, HCV, and syphilis; questionnaires; support for linkage-to-care, care engagement and ART adherence) and contains no biomedical intervention or clinical care (ART prescription or other medical treatment), standard adverse event reporting will not be undertaken. The study team will collect and report all social impacts that are brought to the attention of study staff members. Research staff will be trained to recognize and report social impacts as well as provided with referrals for counseling and social service support, if necessary. Reports of social impacts will be reviewed quarterly or more often, if indicated, and reported to the DAIDS Medical Officer together with any actions that are taken. Social impacts will be summarized and reported to appropriate IRB(s) on an annual basis.

Confidential HIV and STI surveillance reporting will be done according to local regulations. Participants will be reminded of these requirements via the Informed Consent Form.

6.2 Social Impact Reporting

It is possible that participants' involvement in the study could become known to others, and that a social impact may result (i.e., because participants could be perceived as being HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. A social impact that is reported by the participant and judged by the Investigator of Record (IoR) or designee to be serious or unexpected will be reported to the responsible site's IRBs at least annually, or according to their individual requirements. Social impact will be collected and reported on case report forms (CRFs) during regular visits. In the event that a participant reports a social impact, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. While maintaining participant confidentiality, study sites may engage their Community Advisory Board (CAB) in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such a harm.

7.0 STATISTICAL CONSIDERATIONS

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. 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.

7.2 Endpoints

7.2.1 Primary Endpoints

Consistent with the primary study objective to assess the ability of DC-RDS to identify and recruit HIV-infected MSM in the US who are not virally suppressed, the following endpoints will be assessed:

- HIV status at screening for each MSM recruited by DC-RDS (i.e., MSM who complete the first screening visit)
- HIV viral load at screening for each HIV-infected MSM recruited by DC-RDS

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 months after enrollment, the following endpoint will be assessed:

- HIV viral load at 24 months after enrollment

7.2.2 Secondary Endpoints

Consistent with the secondary study objective to assess HIV prevalence and the proportion of men who are virally suppressed by comparing early wave (approximately 1-6) vs. later (deep) wave (approximately 7-12) DC-RDS participants, the following endpoint will be assessed:

- Date and wave of recruitment for each man recruited by DC-RDS

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, 9, 12 and 18 months after randomization the following endpoints will be assessed:

- HIV viral load at 3, 6, 9, 12 and 18 months after enrollment

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 month follow-up

Consistent with the secondary study objective to compare the proportion of men with HIV-hepatitis C virus (HCV) co-infection who are linked to care and who achieve HIV viral suppression 24 months after enrollment between the two study arms the following endpoint will be assessed:

- HCV status at baseline
- HIV viral load at 24 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 months after enrollment the following endpoints will be assessed:

- Self-reported sexual risk behavior (number of male sexual partners, episodes of unprotected anal intercourse [UAI], characteristics of 3 most recent partners) at baseline using a standardized assessment tool
- Age, education, and other socio-demographic measures at baseline
- CD4, HIV viral load and syphilis status at baseline

Consistent with the secondary study objective to compare ART adherence at 24 months and changes in sexual risk behavior, health care utilization, stigma, substance use and mental health between the two study arms over 24 months, the following endpoint(s) will be assessed:

- Self-reported sexual risk behavior (number of male sexual partners, episodes of unprotected anal intercourse [UAI], characteristics of 3 most recent partners) at baseline and 24 months using a standardized assessment tool
- ART adherence at 24 months
- Health care utilization at baseline and 24 months using a standardized assessment tool
- Stigma at baseline and 24 months using a standardized assessment tool
- Substance use at baseline and 24 months using a standardized assessment tool
- Mental health at baseline and 24 months using a standardized assessment tool

Consistent with the secondary study objective to evaluate the feasibility and scalability of the CM intervention package, the following endpoint(s) will be assessed:

- Number of contacts (text message, email, phone, in person) for each participant randomized to the CM intervention arm over follow-up

Consistent with the secondary study objective to compare the experience of linkage to and ongoing HIV care among participants in the two study arms, the following endpoint(s) will be assessed:

- Satisfaction with the CM intervention components, as measured on a Likert scale during a standardized exit interview
- Usefulness of the CM intervention components, as measured on a Likert scale during a standardized exit interview
- Open-ended questions for process evaluation

7.2.3 Exploratory Endpoints

Consistent with the exploratory study objective to use phylogenetic methods to evaluate the relationship between HIV strains in men identified via DC-RDS, the following endpoint(s) will be assessed:

- The phylogenetic relationship between HIV sequences

Consistent with the exploratory study objective to use laboratory assessments to characterize the study cohort and to evaluate the impacts of study interventions, the following endpoint(s) will be assessed:

- Laboratory measures that may include HIV drug resistance, detection of ARV drugs and other assessments

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.

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

Difference in proportion suppressed at 24 months between arms[1]	0.12	**0.18**	0.24
Number randomized	780	**356**	190

[1]Valid for SOC control group viral suppression rates between ~30 – 50%.

Table 3 shows that with the proposed sample size of 2700 MSM we will be able to estimate the proportion of HIV-infected MSM who are unaware of their status and who are not virally suppressed to a precision of approximately +/- 0.04.

Table 3. Precision for estimating the indicated proportions assuming N= 2700 and 20% (540 total) are HIV-infected

Endpoint	Expected proportion	Precision of estimate with proposed sample size
Awareness of HIV-infected status	0.20	+/-0.034
Virally suppressed at enrollment (among HIV-infected)	0.25	+/-0.037

7.4 Random Assignment

HIV-infected MSM who are recruited by the DC-RDS, are eligible and agree to participate in the study will be randomized in a 1:1 ratio to the CM intervention and SOC control arms using randomly-permuted blocks, stratified by site.

The randomization scheme will be generated and maintained by the HPTN SDMC. Additional details regarding the process of randomization will be included in the SSP Manual.

7.5 Blinding

Participants and study investigators will not be blinded to the randomization assignments.

7.6 Data Analysis

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 methods[76] will be reported.

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 months after enrollment. The absolute difference in the probability of viral suppression between the CM intervention and SOC control arms and a 95% CI will be reported. A chi-squared test with a two-sided alpha level of 0.05 will be used for testing the hypothesis:

Ho: No difference in suppression between arms

Ha: Difference in suppression between arms

The analysis will follow the intent to treat principle. If a participant drops out prior to 24 months, their viral suppression status at last study assessment will be used in the analysis. A sensitivity analysis will be conducted to evaluate the effect of different assumptions about the viral suppression status of those who drop out.

As a secondary analyses we will repeat the above for the subgroup of randomized participants who are HCV seropositive at baseline.

7.6.2 Secondary Analysis

We will divide the (approximately 2700) MSM who are recruited into early and later waves (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. A two-sided alpha level of 0.05 will be used for hypothesis testing.

We will also repeat the analysis of HIV viral suppression (described in Section 7.6.1) at 3, 6, 9, 12 and 18 months of follow-up. As in the primary analysis, viral suppression status at last study assessment will be used for participants who drop out prior to a time point. Chi-squared tests with a two-sided alpha level of 0.05 will be used at each time point.

Among the HIV-infected MSM who are enrolled and randomized, we will compare the rates of linkage to care (defined as at least one care visit within 30 days of enrollment) between the CM intervention and SOC control arm. Any randomized participant who drops out of the study prior to 30 days will be counted as "not linked" for the purpose of this analysis. The absolute difference in the probability of linkage between the CM intervention and SOC control arms and a 95% CI will be reported. A chi-squared test with a two-sided alpha level of 0.05 will be used for hypothesis testing. Similarly, we will use a Cox regression model to compare time to first linkage visit between the two study arms. A hazard ratio and 95% CI will be reported. Both analyses will follow the intent to treat principle.

We will also compare the proportion of MSM who are retained in care (defined as at least two care visits [one in each six month interval, with at least 60 days between these visits] over the 24 months after enrollment) between the CM intervention and SOC control arm. Any randomized participant who drops out of the study without at least two care visits as defined above will be counted as "not retained" for the purpose of this analysis. The absolute difference in the probability of retention between the CM intervention and SOC control arms and a 95% CI will be reported. A chi-squared test with a two-sided alpha level of 0.05 will be used for hypothesis testing. The analysis will follow the intent to treat principle.

We will build a multiple logistic regression model to examine the associations between viral suppression at 24 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 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 month value of the measure as the outcome (or most recent assessment for participants that drop out prior to 24 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. The coefficient of the CM intervention arm covariate will be used to quantify the CM intervention effect. An estimate of the CM intervention effect and a 95% CI will be provided for each outcome. Further details will be provided in a separate Statistical Analysis Plan.

Among those randomized to the CM intervention arm we will measure the number of contacts (text message, email, phone, in person) per participant over follow-up. Summary statistics (mean, median, interquartile range, etc.), standardized by the number of months in follow-up, will be provided.

We will summarize the distribution of responses on satisfaction with and usefulness of the CM intervention components from the exit interviews using means, medians and interquartile ranges.

7.6.3 Qualitative Analysis

We will conduct qualitative analysis of all open-ended process evaluation data by coding and analyzing the qualitative data utilizing a qualitative software package for systematic data management (e.g., NVivo) to evaluate participants' and CMs' reactions, preferences and recommendations for treatment interventions.

7.6.4 Exploratory Analysis

Phylogenetic trees will be built using HIV sequences from study participants and other relevant sequences (e.g., controls). If viral networks are identified, we will evaluate the relationship of behavioral, socio-demographic, clinical, and virologic characteristics to viral networks.

If other exploratory laboratory assessments are performed (e.g., drug resistance, ARV drug use, HCV phylogenetics), the HPTN Laboratory Center (LC) will identify specific endpoints for analysis.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent form(s) contained in Appendix IV — and any subsequent modifications — will be reviewed and approved by the HPTN Scientific Review Committee (SRC) and DAIDS Prevention Science Review Committee (PSRC) with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications —will also be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at each study site.

Subsequent to initial review and approval, the responsible IRBs will review the protocol at least annually. The Investigators of Record will make safety and progress reports to the IRBs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. Study sites are responsible for the submission of continuing review documentation to the DAIDS Protocol Registration Office, in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

8.2 Informed Consent

Written informed consent will be obtained from each study participant prior to conducting study-related procedures. Each study site is responsible for developing a study informed consent form for local use, based on the templates in Appendix IV, which describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations.

Participants will document their provision of informed consent by signing the informed consent forms. (Further details regarding DAIDS requirements for documenting the informed consent process are provided in the DAIDS Standard Operating Procedure for Source Documentation.)

All participants will be offered a copy of their informed consent forms.

8.3 Incentives

Pending IRB approval, participants may be compensated for their time and effort for study-required activities, or reimbursed for travel to study-required visits or time away from work for study-required activities. Site-specific reimbursement amounts will be specified in the study informed consent forms.

8.4 Confidentiality

All study-related information will be stored securely at each study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be

stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by NIAID and its contractors; representatives of the HPTN Leadership and Operations Center (LOC), SDMC, or HPTN LC; OHRP or other government and regulatory authorities; or site IRBs.

The HPTN will obtain a Certificate of Confidentiality from the U.S. Department of Health and Human Services that will be applicable for this study. Sites may register under the Certificate through the HPTN LOC once they have obtained local IRB approval for the study. This Certificate protects study staff from being compelled to disclose study-related information by any Federal, State or local civil, criminal, administrative, legislative, or other body.

8.5 Communicable Disease Reporting Requirements

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

8.6 Study Discontinuation

The study also may be discontinued at any time by NIAID, the HPTN, OHRP or other government or regulatory authorities, or site IRBs.

9.0 LABORATORY SPECIMENS AND BIOHARDS CONTAINMENT

Laboratory procedures are described below and in Appendix I.

9.1 Local Laboratory Specimens

Specimens will be collected for testing at the local laboratory. Laboratory evaluations/procedures will include:

- HIV testing (see SSP Manual)
- Syphilis testing
- HCV testing (see SSP Manual)
- CD4 cell count testing
- HIV viral load testing
- Plasma storage

Local laboratories and clinics where testing is performed must be certified under the Continuous Laboratory Improvement Amendment (CLIA-certified) or must be in possession of a CLIA Waiver. Additional local and State guidelines must also be followed.

Each study site will adhere to standards of good clinical laboratory practice, and local standard operating procedures for specimen management including proper collection, processing, labeling, transport, and storage of specimens to the local laboratories. Specimen storage at the local laboratory will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the SSP Manual.

9.2 Laboratory Center (LC) Specimens

Specimens will be collected for testing at the HPTN LC. Laboratory evaluations and procedures will include:

- HIV quality assurance (QA) testing
- Other testing*

*Stored plasma will be used for QA testing and other assessments at the HPTN LC, including cross-sectional incidence testing (to identify participants who are recently infected at Screening) and phylogenetic analysis. Other assessments that may be performed include ARV drug testing; HIV resistance testing; characterization of HIV and HCV and the host response to viral infection). Samples collected in the study may also be used to evaluate assays related to HIV and HCV infection. In some cases, testing will be performed at a commercial laboratory or other laboratory designated by the HPTN LC. These assessments will be performed retrospectively; results will not be returned to study sites or participants (with the possible exception of HIV diagnostic testing, if results obtained at the HPTN LC differ from site results).

9.3 Quality Control and Quality Assurance Procedures

HPTN LC staff will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control (QC) procedures, including proper maintenance of laboratory testing equipment and use of appropriate reagents. HPTN LC staff will follow up directly with site staff to resolve any QC or QA problems identified through proficiency testing and/or on-site assessments.

9.4 QC for HIV Diagnostic Testing

The HPTN LC will perform HIV diagnostic testing for QC. Algorithms for HIV diagnostic testing are provided in the SSP Manual.

9.5 Retrospective HIV RNA Testing

If a participant is found to be HIV-infected at the S1 visit, but does not return for the S2 visit, the stored plasma sample will be used to determine viral load (HIV RNA) in order to provide complete data for the primary DC-RDS-related objective.

9.6 Phylogenetic Analysis

Phylogenetic methods will be used to explore the patterns and dynamics of HIV transmission. HIV sequencing will be performed at the HPTN LC or another laboratory designated by the HPTN LC. HIV sequencing will be performed by bulk (population) sequencing; next generation/deep sequencing may also be performed. The HPTN LC will determine the methods used for phylogenetic analysis (e.g., the HIV genomic regions analyzed, use of local and other control sequences, methodology used for data analysis).

9.7 Specimen Storage and Possible Future Research Testing

Study site staff will store all plasma specimens collected in this study at for at least three years after the end of the study (completion of the last study visit). In addition, study participants will be asked to provide written informed consent for their plasma specimens to be stored after the end of the study for possible future testing related to HIV and HCV infection and evaluation of laboratory assays relevant to the study objectives. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed after all protocol-related testing has been completed; sample destruction must be coordinated with the HPTN LC and HPTN SDMC.

9.8 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the US CDC. All infectious specimens will be transported in accordance with US regulations (42 CFR 72).

9.9 Resistance Testing at Local Laboratories.

HIV resistance testing may be performed at local laboratories for clinical management using locally-available resistance test methods. Study specimens may not be used for this testing; additional specimens must be collected for this testing. Resistance testing may also be performed at the HPTN LC or a laboratory designated by the HPTN LC using stored specimens; results of this testing will not be returned to study sites or study participants.

10.0 MODELING COMPONENT

10.1 Background and Prior Research

Mathematical models of HIV transmission are widely used to understand the dynamics of HIV transmission, to assess the population-level impact of HIV prevention and treatment interventions and to inform policy decisions.[77] They are also increasingly and innovatively being used at different stages of the clinical trial process: to inform product development, to inform the design of optimal combination prevention, to inform the design and conduct of large community-based clinical trials, and to interpret and help generalize results to the wider population.[78] Models of HIV transmission amongst MSM have been used to estimate the impact of role segregation (taking only the insertive or receptive role in anal intercourse),[79-81] and serosorting (having anal sex only with MSM of the same HIV status),[82, 83] which both lead to lower overall HIV prevalence. Models have also been used to understand the racial disparities in HIV prevalence seen amongst MSM in the US,[84] which are related to preferential mixing by race, and differences in access to care and treatment. Models have been used to estimate the impact of pre-exposure prophylaxis for MSM in the USA[85] and Peru,[86] informed by effectiveness estimates from the iPreX trial of PrEP for MSM. Modelling has also been used to estimate the likely impact of increasing HIV testing and treatment amongst MSM. For example, modeling has been used to predict a moderate impact of increased testing frequency alone for MSM,[15, 87] to estimate the impact of behavior change following HIV testing[88] and to predict a more substantial impact from increased testing coupled with immediate ART treatment for MSM.[15, 89, 90]

In the current study, models will be used to estimate the likely population level impact on HIV transmission of the increased rates of identification of HIV-infected non-virally suppressed MSM and the increased level of viral suppression achieved in the trial, and to estimate the effect of the different trial components, which aim to increase the identification of unsuppressed HIV-infected MSM and increase linkage to care, ART initiation and retention in care.

10.2 Rationale

Mathematical modelling will be used to translate the results of the study and estimate the potential population-level impact of the tested CM intervention on HIV, since the trial does not include HIV incidence as an endpoint and will measure the impact of the CM intervention at an individual rather than a community level. Rather than measuring the impact of the CM intervention upon HIV incidence, the first main objective of the study is to measure the success of the DC-RDS strategy in finding MSM who are not virally suppressed (primary objective), while also capturing useful information about the risk profile (behavioral, socio-demographic and clinical) of the population reached and retained at different stages of the treatment cascade (secondary objective). 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 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).

Given the focus on treatment outcomes and the endpoint of viral suppression, and the fact that the CM intervention can influence multiple outcomes on the causal HIV prevention pathway among HIV-infected MSM (e.g. increased initiation and retention in treatment, changes in sexual behavior), it is difficult to understand the prevention potential of the individual-level CM intervention on population-level HIV incidence based on the trial results alone. Mathematical models are needed to translate the results of the CM intervention components implemented in this

study into estimates of the potential population-level impact of the combined CM intervention package on future HIV acquisition and transmission, taking into account the specific risk profile of those adopting the CM intervention and the existing epidemiological and prevention contexts where the interventions are taking place.

Models can also be used to estimate the level of treatment-as-prevention efforts required to reduce HIV incidence at the population level by a substantial amount as rapidly as possible, and to assess whether the results of this trial in terms of CM intervention uptake, retention, adherence, and the risk profile of the population reached and responding favorably to the CM intervention warrant roll-out of the CM intervention to the wider MSM population.

10.3 Model Population and Setting

The modelled population will be all sexually active MSM (both HIV-infected and HIV-uninfected) in each of the four different sites included in the trial.

10.4 Main Model Outcomes

The main model outcomes include the following:

- Predicted population-level reduction in incidence and prevalence achieved by the CM intervention, and by individual components of the CM intervention (HIV testing, ART uptake, retention in care and viral suppression) over 2, 5 and 10 years at each site.

- Predicted preventable fraction (PF): The fraction of new HIV infections averted by a given CM intervention package, or its independent components, over a fixed time period

- Estimated level of viral suppression required to reduce HIV incidence at each site by 10%, 20%, 30%, and 50% over 2, 5 and 10 years.

- Estimates of whether or not the CM intervention would be likely to result in HIV elimination (HIV incidence less than one new HIV infection per 1000 people per year[91]) at each site, and the time taken to reach this elimination threshold, both with achieved levels of viral suppression, and for the different levels of viral suppression required to meet incidence reduction targets.

- Population attributable fraction (PAF): The contribution of different risk groups or risk factors to HIV transmission over different time periods.

10.5 Modeling Stages

We will develop and analyze a dynamical, deterministic compartmental model of sexual HIV transmission and HIV prevention among MSM in different US settings, and use it to estimate the impact of the CM intervention at the population level.

For each setting, the modeling study will include a number of stages:

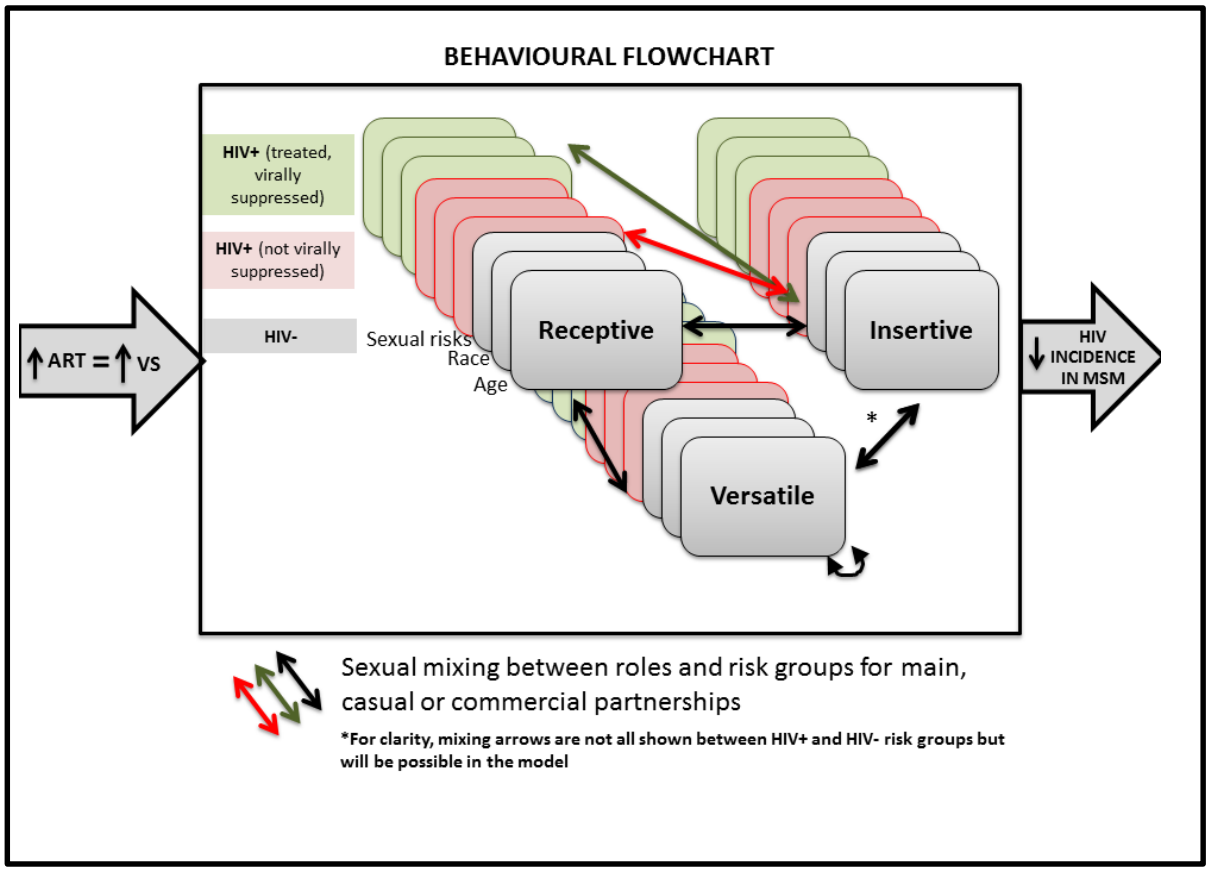
- Model development and coding
- Model parameterization
- Model calibration and fitting to HIV prevalence and incidence data from various site specific sources
- Model analysis: estimation of CM intervention impact, including uncertainty and sensitivity analysis

More details about the different stages are given in the following sections.

10.5.1 Model Development and Coding

The proposed model is a dynamic, deterministic compartmental model which describes HIV transmission via anal sex between and among different risk groups of MSM, as well as rates of HIV progression and levels of testing and treatment over time. Within the model, the MSM population will be divided into different categories stratified by age, race, sexual risk activity (e.g. rate of partner acquisition, frequency of sex acts)[92, 93] and sexual role behavior (exclusively insertive, exclusively receptive, or versatile in anal sex) (Figure 3).[80, 94]

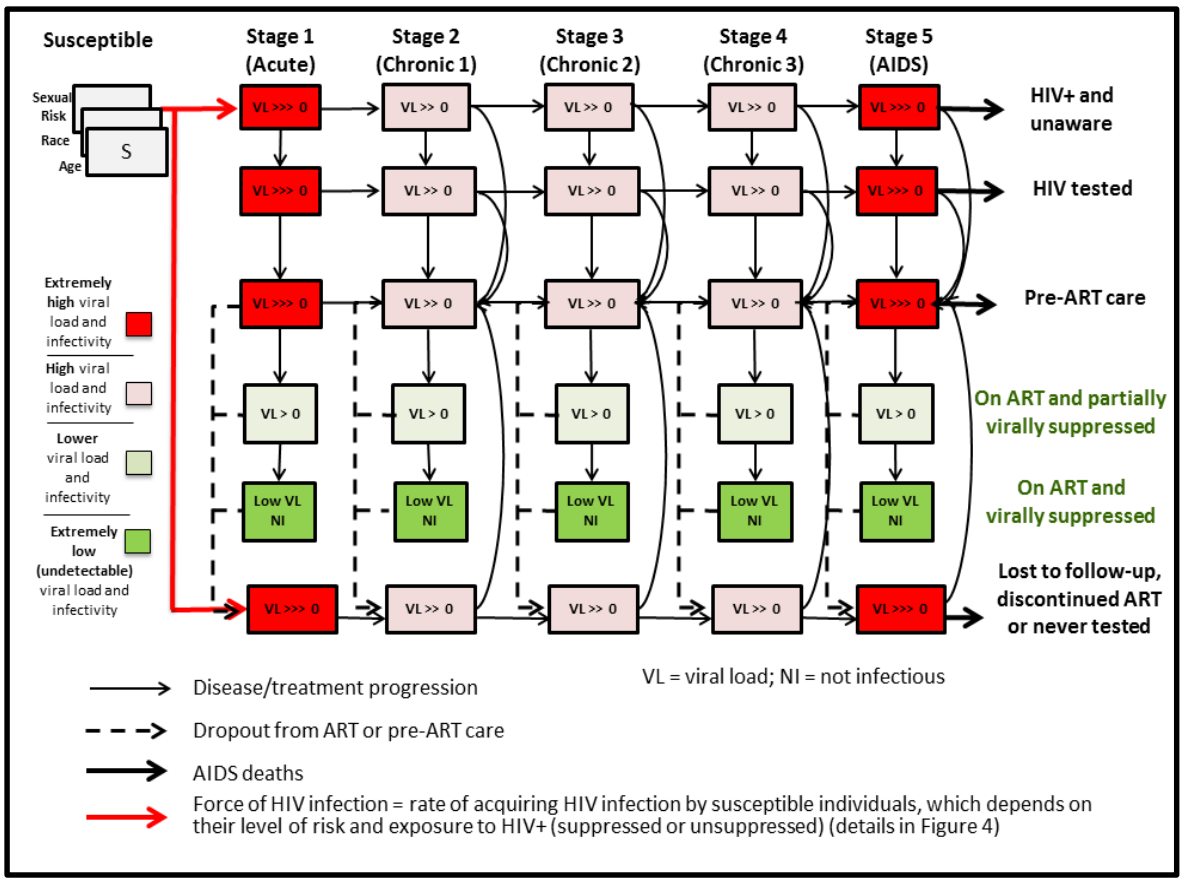
Figure 3: Behavioral Groups and Sexual Mixing in the Model.



MSM are divided into different groups relating to sexual role behavior (exclusively insertive, exclusively receptive, or versatile in anal sex), age, race and sexual risk activity. MSM in each of these groups may be uninfected with HIV (gray), infected and not virally suppressed (red; highly infectious), or infected, treated and virally suppressed (green; reduced infectiousness). Sexual mixing between these groups will be informed by data on mixing patterns by age, race, sexual risk and sexual role. As ART coverage increases (i.e. the proportion of sexual partners on ART increases), HIV viral load will decrease (viral suppression increases) and so HIV incidence will decrease.

In the model, HIV infection and progression will be modelled as a number of discrete stages through which MSM move – susceptible (uninfected), acute HIV infection (stage 1), chronic HIV infection, divided into three stages (stages 2-4), and AIDS (stage 5; Figure 4).[95] This staging allows the model to reflect changes in infectivity, CD4 levels and symptoms which occur as a function of time since infection, and to capture historical changes in the timing of treatment initiation. HIV-infected MSM with acute infection or AIDS will have increased infectivity, and those on ART and virally suppressed will have reduced infectivity (Figures 3 and 4). HIV-infected MSM may move between different categories reflecting their testing and treatment status, including those unaware of their HIV positive status, those tested, linked into pre-ART care, those on ART and partially or fully virally suppressed and those who are lost to follow-up, have discontinued ART and those living with HIV who have never been tested. This last category contains individuals who may also initiate ART when they present with symptoms (Figure 4).

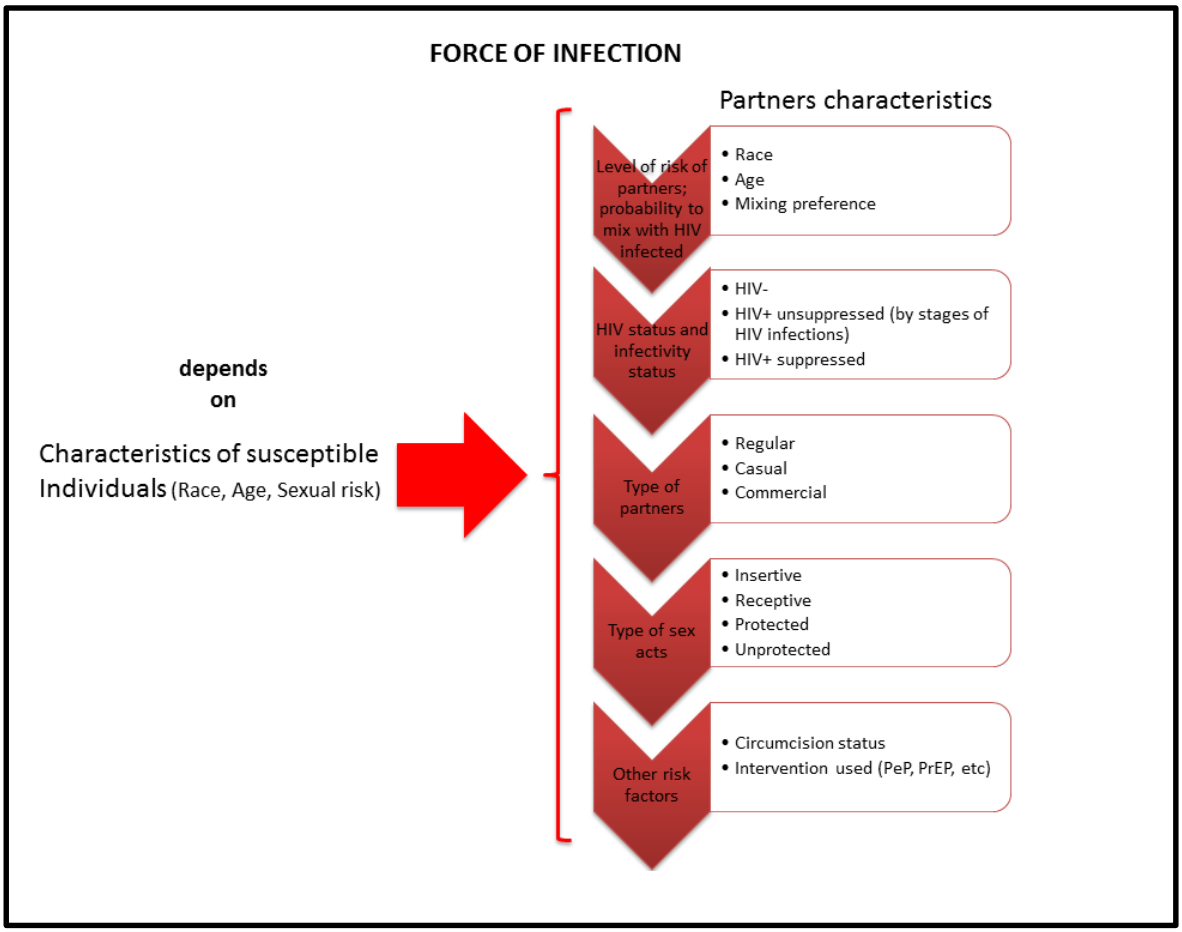
Figure 4: Infection and Treatment States.



MSM in the model are divided into separate categories by infection and treatment status. Infected MSM are divided by infection stage, with the chronic phase subdivided into several stages (reflecting CD4 levels when untreated) to allow more accurate timing of AIDS, appearance of symptoms and ART initiation and modelling historical increases in treatment which was based on CD4 levels. MSM on ART have greatly reduced infectivity when they are virally suppressed. The level of infectiousness is indicated in pink/red/green. MSM start ART either due to presenting symptoms or following testing.

The force of HIV infection (or per capita HIV incidence rate) for susceptible MSM will be estimated (following calibration, details below) based upon the frequency and type of sex acts (insertive/receptive) they have, as well as condom use with different types of partner (main, casual and commercial), their circumcision status, PrEP and PEP use, who their sexual partners are likely to be (based upon mixing preferences related to age, race, sexual risk activity and serostatus and data on the proportion of sexual partners resident inside and outside of the study community), and levels of HIV prevalence and ART use among those partners (Figure 5). To capture the impact of other STIs upon HIV transmission risk, syphilis prevalence measured at baseline will be used together with published estimates of the increased risk of HIV transmission in the presence of syphilis to estimate associated increases in HIV transmission in each setting, assuming stable syphilis prevalence. The final model structure will depend upon the site-specific data available (from the trial and other complementary sources) to determine parameters and also upon important identified sources of heterogeneity.

Figure 5: Force of Infection.



This figure summarizes the different factors which contribute to the force of infection (per capita incidence rate), including characteristics of the susceptible MSM and of their sexual partners.

The model will incorporate the effects over time of past and existing interventions (e.g., increases in condom and ART use), and future interventions (the CM intervention and standard of care, including associated levels of linkage to care, ART initiation and adherence and retention in care), upon HIV susceptibility, transmissibility and rate of disease progression. Changes in levels of HIV testing will also be represented, as will documented changes in sexual behavior (including number and type of partners and sexual mixing patterns).

The model will consist of coupled nonlinear ordinary differential equations and will be coded with a flexible programming language (e.g. C++).

10.5.2 Model Parameterization

The data required to inform model parameters and calibrate the model cover five main domains: demography, sexual behavior, natural history of HIV, intervention, and epidemiological HIV data. This information should ideally be obtained from representative samples of the population. We will use data from the trial (which may need to be standardized to reflect the wider MSM population), and we will also comprehensively review and make use of other relevant sources of data such as HIV surveillance data, the published literature, systematic reviews and official reports. The trial will provide data to inform the modelling of future interventions, including data on the demography, sexual behavior, prior HIV testing, HIV prevalence, viral status, and ART use of those recruited through DC-RDS. The trial will also provide estimates of the proportion of people linking to and retained in care, initiating ART and achieving viral suppression, with and without the CM intervention package. In addition, the trial will provide data on the demographic and risk profiles of those retained at each stage of the HIV care cascade. Complementary data from other sources will be needed to inform modelling of past behavior and interventions and to characterize the wider MSM population at each site (including demographic, sexual behavior and HIV testing data). Other data will also be required to model the progression of HIV and effectiveness of different interventions, and to capture historical changes in behavior and ART coverage. Likely sources of data to inform the CM intervention and standard of care scenarios are summarized in Table 4; the final data sources used may vary depending upon the exact sites used for the trial.

Table 4. Model parameters and likely data sources

Data Domain	Parameters	Trial Data Used	Other Data Used
Demography	Age composition, natural death rates, MSM population size, migration	RDS-derived estimates of population size, age, mobility data, data on whether sex partners are resident inside/outside the community	Age composition: overall for national sample (NHBS); Natural death rates: National Vital Statistics reports; total population size: US Census data; Proportion of people reporting same-sex sexual activity: National Survey of Family Growth (NSFG)
Sexual Behavior	Number and type of male anal sex partners (per unit time), frequency of insertive and receptive anal sex with different partners, preference for partners by age, race, HIV status and sexual activity, role behavior, condom use with different partners. Changes in these behaviors over time	Number of partners and sex acts, role behavior, condom use at baseline (RDS + CM intervention cohort) and after 24 months (CM intervention cohort only), partner characteristics at baseline (RDS + CM intervention cohort)	Number of main and casual partners last year: Overall estimate from CDC NHBS surveys for MSM 2005, 2008, 2011; overall number of male partners last year: NSFG, national estimate; condom use at last sex act: overall estimate from NHBS surveys 2005, 2008, 2011; levels of consistent condom use: NHBS individual sites 2005, 2008, 2011; role behavior[92]
Natural History of HIV	Duration, probability of infection per sex act (by role), infectivity by HIV viral load	(no trial data will be used)	Duration of different stages of infection: European cohort studies[96] Relative infectiousness of different stages of infection: published analyses [97] Probability of infection per anal sex act: published literature and existing systematic reviews[97-99] Infectivity by HIV viral load:[15, 100-102]

Data Domain	Parameters	Trial Data Used	Other Data Used
CM intervention and SOC	Rates of HIV testing, linkage to care, ART initiation, viral suppression; PrEP and PEP use; changes in these over time and differences between study arms. Retention in care and ART adherence. Loss to follow-up. Effectiveness of male circumcision, condoms, ART, PrEP in reducing infectiousness	Current levels PrEP and PEP use, HIV testing, ART coverage in RDS sample; levels of HIV testing post-recruitment among RDS sample; linkage to care, ART initiation, adherence, retention in care, viral suppression for each arm of the trial, by risk group, and loss to follow-up.	Testing: CDC NHBS surveys for MSM (for NHBS sites) Linkage to care, ART initiation, viral suppression: CDC MMWR reports Published literature and systematic reviews on effectiveness of male circumcision,[103] condoms,[104, 105] ART, PrEP
HIV Epidemiology	HIV prevalence and incidence, changes over time, distribution of transmission by sources of infection; distribution among treated and untreated	HIV prevalence in RDS population HIV incidence estimates using laboratory assays (if conducted) Phylogenetic analysis Baseline distribution of treated and untreated HIV-infected; both suppressed and unsurpassed	Prevalence: CDC NHBS surveys for MSM 2005, 2008, 2011 (for NHBS sites) Incidence: CDC estimates for MSM 2005 (selected NHBS sites)

MMWR, Morbidity and Mortality Weekly Report; NHBS, National HIV Behavioral Surveillance; NSFG, National Survey of Family Growth.

For each model parameter, a most likely value and a range of plausible values (*a priori* range) will be obtained.

10.5.3 Model Calibration and Fitting

The model, including past and current levels of interventions, will be calibrated to available HIV prevalence and incidence data over time (which is representative of the sites modelled) within a Bayesian framework where *a priori* information on the key parameters from available data sources is updated through a comparison of the model simulations and epidemiological HIV data.[106] The parameter ranges constructed in the model parameterization stage will be exhaustively sampled and explored at the calibration stage, using state of the art fitting methods previously used[107-109] in order to identify multiple parameter sets that agree with the epidemiological HIV data (HIV prevalence and incidence), producing a set of model predictions which reflect HIV patterns by risk group in the target population while taking into account uncertainty in parameter assumptions. This set of simulations will form our baseline scenario and baseline parameter sets. As per standard procedure in modelling studies ,[94, 95, 107, 108, 110] this calibrated set of simulations will also produce the necessary baseline estimates of population level HIV incidence required to subsequently be able to assess the impact of scaling up future interventions.

10.5.4 Model Analysis

The calibrated model for each site will be used to conduct the following analyses: (1) assess the population level impact of the overall study strategy on HIV incidence and prevalence, and the preventable fraction of HIV infections averted; (2) assess the population level impact of the individual components of the CM intervention (including HIV testing, ART uptake, retention in care, viral suppression) on HIV incidence and prevalence and the preventable fraction of HIV infections averted by these individual components; (3) estimate the level of viral suppression required to reduce HIV incidence at each site by 10%, 20%, 30%, and 50% over 2, 5 and 10 years; (4) estimate the likelihood of and time taken to reach HIV elimination; (5) estimate the PAF for different risk groups, the stage in the cascade of care and the risk factors over different time periods; (6) uncertainty and sensitivity analyses.

10.5.4.1 Overall CM Intervention Impact

The model will be run for each site under two alternative scenarios, standard of care (baseline) and CM intervention, with levels of testing, linkage, ART initiation and retention, and viral suppression going into the future informed by the levels measured in each arm of the trial (table 1). Predicted overall CM intervention impact will be determined by comparing the predicted cumulative HIV incidence, HIV incidence rate and HIV prevalence in the CM intervention and baseline scenarios over 2, 5 and 10 years, with all trial components included in the intervention arm. This will yield estimates of the impact of the total CM intervention package on population-level HIV incidence and prevalence, and the preventable fraction PF(dt) of HIV infections. In these analyses we will take into account differences in CM intervention coverage and uptake by risk group. Each modelling outcome will be presented as the mean, median and uncertainty range (95% percentiles of the model predictions based on the multiple posterior parameter sets).

10.5.4.2 Impact of Individual CM Intervention Components

We will then use the models to estimate the impact of the observed independent CM intervention components, by running additional model scenarios in which only some of the CM intervention components (increased rates of HIV testing, increased linkage, ART uptake, retention in treatment and viral suppression) are included, and comparing these with the baseline model in the same way as for the full CM intervention model, above, to estimate the reduction in incidence and prevalence and the PF associated with each CM intervention component and combination of components. Each modelling outcome will be presented as the mean, median and uncertainty range (95% percentiles of the model predictions based on the multiple posterior parameter sets).

10.5.4.3 Required Viral Suppression to Achieve Incidence Reduction Targets

We will also use the models to estimate the level of viral suppression and associated CM intervention efforts that need to be achieved in order to reduce HIV incidence in the MSM community by 10%, 20%, 30%, and 50% over 2, 5 and 10 years.

10.5.4.4 HIV Elimination

We will estimate whether HIV is predicted to be eliminated if the CM intervention were carried on into the future for each site, both with achieved levels of viral suppression, and for the different levels of viral suppression required to meet the incidence reduction targets (10%, 20%, 30%, and 50% reduction over 2, 5 and 10 years). Elimination is defined as HIV incidence going below one new HIV infection per 1000 people per year.[91] Where elimination is predicted, we will estimate the predicted time taken to reach the elimination threshold.

Each study outcome will be presented as the mean, median and uncertainty range (95% percentiles of the model predictions based on the multiple posterior parameter sets).

10.5.4.5 Population Attributable Fraction (PAF)

We will determine the main drivers of HIV acquisition and transmission in the MSM populations studied by calculating the short and long term transmission PAF.[111, 112] The PAF(dt) will be derived by comparing the number of new infections using two defined risk parameters: 1) assuming that the given risk factor increases risk of HIV acquisition or transmission or the relevant risk behavior; 2) assuming no increase in risk associated with the factor under study. The key risk groups for whom we will calculate PAFs will be: sexual role groups (insertive or receptive, versatile), untested MSM, and HIV-infected MSM who not virally suppressed.

10.5.4.6 Uncertainty and Sensitivity Analyses

We will conduct an uncertainty analysis using the multiple calibrated simulations to assess the influence of key epidemiological and intervention factors/parameters (in CM intervention and SOC control arms) on impact predictions (using a technique such as partial rank correlation), and determine under which conditions a CM intervention will have the largest impact (using techniques such as regression trees analysis).

We will conduct a sensitivity analysis to determine the influence on the impact estimates (incidence and prevalence reduction and PF) of key parameters such as the evolution of the SOC over time, and determine a threshold of high sensitivity where impact is considerably reduced.

11.0 ADMINISTRATIVE PROCEDURES

11.1 Protocol Registration

Initial Registration of the protocol by the DAIDS Protocol Registration Office (PRO) is required prior to implementation of this protocol. As part of this process, each site must have the protocol and protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. In the case of Initial Registration, site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO. Sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Following Initial Registration, any full protocol amendments require submission of a protocol registration packet to the DAIDS PRO as described above; however, the DAIDS PRO will not review and approve site-specific ICFs. Sites will receive a Registration Notification when the DAIDS PRO receives a complete registration packet. There may be cases where a site submits as their Initial Registration a protocol amendment (Version 2.0 or higher of a protocol); in such cases, the instructions for Initial Registration will be followed.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which can be found at http://rsc.tech-res.com/protocolregistration/.

11.2 Study Activation

Pending successful protocol registration and submission of all required documents, the HPTN LOC staff will "activate" a site. Study implementation may not be initiated until a study activation notice is provided to the site by the HPTN LOC. In addition, if study "activation" is determined to be necessary for any subsequent amendments, study implementation may not be initiated until a study activation notice is provided to the site by the HPTN LOC.

11.3 Study Coordination

Study implementation will be directed by this protocol as well as the SSP Manual. The SSP Manual will outline procedures for conducting study visits; data and forms processing; social harm assessment, management and reporting; and other study operations.

Study CRFs and other study instruments will be developed by the protocol team and HPTN SDMC. Data will be transferred to the HPTN SDMC for data entry, cleaning, reporting and analysis. Quality control reports and queries will be generated and distributed to the study sites on a routine schedule for verification and resolution.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and social harm incidence will be monitored closely by the team as well as the HPTN Study Monitoring Committee (SMC). The Protocol Chair, DAIDS Medical Officer, Protocol Biostatistician, SDMC Project Manager, and HPTN

LOC representatives will address issues related to study eligibility and social harm management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

11.4 Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- Verify compliance with human subjects and other research regulations and guidelines;
- Assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- Confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, HPTN SDMC, HPTN LC, NIAID, site IRBs/ECs, and US regulatory authorities (OHRP). A site visit log will be maintained at each study site to document all visits.

11.5 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s) and the DAIDS Regulatory Support Center (RSC) prior to implementing the amendment.

11.6 Investigator's Records

All site Investigators of Record (IoR) will be responsible for maintaining, and storing in a secure manner, complete, accurate, and current study records throughout the study. Under HHS regulations, the IoR is required to retain all study records relating to research for at least three [3] years after completion of the research, or longer if needed to comply with local regulations. Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects;
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan;
- All analysis of identifiable private information described in the IRB/EC-approved research plan;
- Primary analysis of either identifiable private or de-identified information.

Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, CRFs, notations of all contacts with the participant, and all other source documents.

11.7 Use of Information and Publications

Publication of the results of this study will be governed by the HPTN Manual of Operations. Any presentation, abstract, or manuscript will be submitted to the HPTN Manuscript Review Committee for review prior to submission.

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APPENDICES

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							
Informed consent	X		X				
Release of medical information			X				
Locator information	X		X		I	X	X
Questionnaire administration (see Appendix II)	X	X	X				X
Recruiter Training	X						
Coupon Reimbursement		X					
Social impact assessment	X	X			I	X	X
Pre- and post-test HIV counseling, including HIV/STI risk reduction counseling	X	X					
Offer of partner HIV counseling and testing			X			X	X
Coupon disbursement	X						
Case manager (CM) intervention			I		I	I	I
Exit interview							X
Clinical Evaluations/Procedures							
Blood collection	X	X[3]				X	X
Syphilis treatment, if indicated		X					X[9]
HCV treatment or referral, if indicated		X					
Laboratory Evaluations/Procedures							
HIV testing[2]	X	X[11]					
Hepatitis C virus testing[2]	X						
Syphilis testing[4]	X						X
CD4 cell count testing		X[5]		X[6]		X[7]	X
HIV viral load testing		X[5]		X[6]		X	X
Plasma storage[8]	X	X[10]				X	X

Note: Monthly visits will be defined as a predetermined number of weeks, as described in the SSP.

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

[1]Monthly contact is only provided to participants in the CM intervention arm; these interactions may be conducted in person or by phone, text message or email.

[2]Procedures for HIV and HCV testing are described in the SSP Manual.

[3]Blood will be collected at the S2 visit for all HIV-infected individuals and for those with discordant/inconclusive HIV test results (see SSP Manual). Blood will not be collected for HIV-uninfected individuals (those who have no reactive or positive HIV test results from the S1 visit).

[4]Syphilis testing will be performed using blood specimens according to local standards.

[5]CD4 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 (see SSP Manual). .

[6]CD4 cell count and HIV viral load data will be collected from participant medical records, if available.

[7]CD4 cell counts at follow-up visits may be used in the assessment of cross-sectional HIV incidence

[8]Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9.2). These assessments will be performed retrospectively; results will not be returned to study sites or participants except as noted in Section 9.2.

[9]If the syphilis test is positive at the final study visit participants will be recalled for an ad hoc visit to receive the results and be referred for care.

[10]Plasma will be stored at the S2 visit for all HIV-infected individuals and for those with discordant/inconclusive HIV test results. Plasma will not be stored at the S2 visit for HIV-uninfected individuals (those who have no reactive or positive HIV test results from the S1 visit).

[11]Additional HIV testing will be done at the S2 visit if test results from the S1 visit are discordant/inconclusive (see SSP Manual).

Appendix II: Schedule of Questionnaire Domain Administration

Questionnaire Domain	Screening (DC-RDS participants)	Enrollment (M0) (Intervention participants [CM Intervention and SOC control arms])	Final (M24) (Intervention participants[CM Intervention and SOC control arms])
Demographics	X (S1)		
PrEP/PEP/ART use	X (S1)		
HIV testing history	X (S1)		
Engagement in LGBT community	X (S1)		
Post-recruitment questions*	X (S2)		
Health care utilization	X (S1)		X
Sexual matrix module / sexual risk behavior	X (S1)		X
Stigma	X (S1)		X
Substance use and mental health		X	X
Medication adherence			X

*****These questions will only be asked of those who were given coupons to distribute and who distributed, or attempted to distribute, them.

APPENDIX III

RECRUITER INFORMATION SHEET

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

HPTN 078

Version 1.0
October 8, 2015
DAIDS Document ID: 11995

RECRUITER INFORMATION SHEET
(to be offered to all MSM who are given coupons to dispense to their peers)

Sponsored by: Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH).

INVESTIGATOR OF RECORD: *[Insert Name*]

PHONE: *[Insert Number]*

We would like to learn more about the population of men who have sex with men (MSM), issues that affect their health, their risk for HIV and other infections. It is very important for us to learn from a large number and variety of MSM, and we are asking you to help us to reach and invite MSM who may be interested in participating. We hope to use what we learn from you and the people you invite to help develop new and improved programs and services for MSM.

The benefits to you include:

- Reimbursement for recruiting other MSM

The benefits to those you invite include:

- Free, confidential HIV, Hepatitis C virus, and syphilis testing
- Reimbursement for participating
- Reimbursement for recruiting other MSM

Who to Recruit

We're going to give you coupons to give to other MSM so that they can participate in the study too. You should give the coupons to MSM you know and have seen at least once in the past 30 days. You should only give the coupons to MSM who are 16 years old *[Note to sites: change this to "18 years old" if your IRB does not allow you to recruit minors]* or older and who live in or around [*insert site location]*. We are trying to recruit diverse participants into this study, so we would appreciate it if you could distribute the coupons to MSM with different characteristics, rather than just MSM whom you know through the same social group. Since people only participate once, don't give the coupons to anyone who has already participated.

Most importantly, you should NOT give the coupons to strangers. The MSM you recruit will have to bring in their coupons and answer questions to determine if they are eligible to participate.

If one of the people you invite declines and does not accept a coupon, you may use the same coupon to try to invite someone else.

Coupons

To participate, everyone must have a valid coupon. Be sure to tell the MSM you give a coupon to that he needs to have the coupon with him when he comes in. The first thing we'll do is check to see if his coupon is valid.

Your coupons cannot be replaced if they are lost or stolen or if the person you recruited is not a MSM. Each coupon has a date when it expires, and after that date it can't be used anymore. Please make sure the men you invite to the study are aware of this.

The coupons provide the study address and phone number. [*Sites to add information here about whether participants need to make an appointment, or if there are drop-in hours, or both.*] Every coupon has a unique number so we know if the coupons you handed out are brought back to the clinic.

Participation

Please be sure to inform the men you invite about the benefits (listed above) and confidentiality of the activities. They will participate in the same activities you participated in today (blood tests and questionnaires). Be sure to tell the people you recruit to come in at a time when they can expect to be able to complete the whole process, which takes about [*site to complete]*. Anyone who brings a valid coupon to the site, is a MSM, has blood taken and completes the questionnaires will be given [*site to add amount]*.

Payment

You will receive a small payment for your assistance with helping to invite other MSM to the study. You will receive [*site to add amount]* for each MSM who brings one of your valid coupons to the clinic. But, it's not guaranteed that you will get the payment just for recruiting someone.

- You will not be paid for recruiting someone who is not an MSM.
- You will not be paid for recruiting someone who is 15 years old or younger. *[Note to sites: change this to "17 years old or younger" if your IRB does not allow you to recruit minors]*
- You will not be paid for recruiting someone who has already completed the tests and questionnaires for this study.
- You will not be paid for someone who does not come to the study site.

Not everyone in this study will have the opportunity to recruit others. Once we recruit as many MSM as we need for this study, no more coupons will be given out.

Recruiter Questionnaire

When you return for your payment, we will ask you some questions about the people who may have declined the coupons and why they may have declined.

Procedures

For you to receive your payment, it is required that you return in person to the office. We will only pay you, so do not send someone else to receive your money. This allows us to make sure that you receive the payment you are owed.

Wrap-up: Do you have any questions? Okay, remember, give the coupon to MSM you know. Thanks for helping us!

RECRUITER REMINDERS

Who to Recruit

- Give the coupon to someone you know, such as a friend, relative or someone you are close to, and not a stranger.
- Give the coupon to someone who lives in your city.
- Give the coupon to someone who has not participated already.
- Give the coupon to a MSM who is 16 years old or older [*Note to sites: Change this to "18 years old or older" if your IRB does not allow you to recruit minors*] or lives in or around [*insert site location*].
- Try to give the coupons to MSM with different characteristics, rather than just MSM whom you know through the same social group.

Coupons

- You will not get replacement coupons if your coupons are lost or if the person you recruit is not a MSM.
- Everyone has to have a coupon to participate. Tell the people you recruit to have the coupon with them when they come in.
- Coupons will expire and cannot be used (given out or brought in) after that date.

Payment and Time for Participation

- Everyone who brings a valid coupon, is an MSM, has blood taken and completes a questionnaire will get [*site to add amount*].
- The whole process for participation takes about [*site to complete*] hours.

Payment for Recruiting

- You will get paid [*site to add amount*] for each person who you successfully recruit; the money is not guaranteed just because you give someone a coupon.
- You will not be paid for someone who does not come to the site. If they don't come to the site, they won't get paid and you won't get paid.
- We can't tell you who came in with a coupon from you.
- We will only pay you—don't send someone else to receive your money.

Recruiter Questionnaire

- We ask questions so that we can identify you again when you come to get your payment.
- We also ask questions to understand why some people may decline coupons.

APPENDIX IV

INFORMED CONSENT TEMPLATES

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

HPTN 078

Version 1.0
October 8, 2015
DAIDS Document ID: 11995

SCREENING INFORMED CONSENT FORM

Sponsored by: Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH).

PRINCIPAL INVESTIGATOR: *[Insert Name*]

PHONE: *[Insert Number]*

INTRODUCTION

You are being asked to take part in a research study that is designed to find the best way to find men who have sex with men (MSM) and offer them HIV testing. Joining this study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason. This research study is for MSM who may be at risk for getting Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS.

Before you decided whether to join the study, we would like to explain the purpose of the screening, the risks and benefits to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the screening. Once you understand the screening, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

Before you learn about screening, it is important that you know the following:

- Your participation is voluntary. You do not have to take part in any of the screening tests, questionnaires or procedures.
- You may decide not to participate in screening, or you may decide to leave the screening at any time.
- If you decide not to take part in the screening, you can still join another study at a later time if there is one available and you qualify.
- If you decide not to take part in the screening, or decide to stop participating at any time, there will be no penalty or loss of the normal benefits provided to you at our clinic.

PURPOSE OF THE SCREENING

The purpose of the screening activities is to find sexually active MSM using a technique called "respondent driven sampling." In respondent driven sampling, 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.

Information from the screening activities will be used to prevent the spread of HIV in the MSM community.

SCREENING PROCEDURES

If you agree to participate, you will be asked to participate in two screening visits.

Screening Visit 1

Screening Visit 1 will happen after you read, discuss, understand, and sign this form. We will help you understand the form and answer your questions before you sign this form. The procedures done during Screening Visit 1 will take about [*sites to fill in the amount of time]* hours.

During this visit:

- We will confirm where you live and how to contact you.
- We will ask you to complete a questionnaire. This questionnaire will ask you about yourself (like your age and race), your sexual behavior and partners, use of HIV drugs, HIV testing history, health care use, involvement in the lesbian, gay, bisexual and transgender (LGBT) community, and stigma you may have faced because you are an MSM.
- We will ask you if you have had any problems because you are a part of this screening.
- We will talk to you about HIV and other sexually transmitted diseases and give you information to help you protect yourself from getting them.
- 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.
- We will collect a small amount of blood (approximately 20 mL = about 4 teaspoons) to store for additional laboratory testing. These tests may include testing for the presence of HIV or HIV drugs in your blood and will be used to learn more about the HIV virus if you are HIV-infected. These tests will give us information about the HIV virus, how the virus spreads in the community, and how the body responds to HIV infection. If you have

hepatitis C virus infection, the blood may also be used for testing to learn more about the hepatitis C virus and how it spreads in the community.

- We may give you coupons and ask you to invite MSM you know to come to the clinic for screening.

Screening Visit 2

The procedures done at Screening Visit 2 will take about [*sites to fill in the amount of time*] hours.

During this visit:

- We will give you the results of your HIV, hepatitis C virus and syphilis tests. If you have any of these diseases, you will be referred for treatment [*sites to add specifics about how this will take place at their site*].

- 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 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).

- We will also collect a small amount of blood (approximately 20 mL = about 4 teaspoons) to store for additional laboratory testing. These tests may include testing for the presence of HIV or HIV drugs in your blood and will be used to learn more about the HIV virus if you are HIV-infected. These tests will give us information about the HIV virus, how the virus spreads in the community, and how the body responds to HIV infection. If you have hepatitis C virus infection, the blood may also be used for testing to learn more about the hepatitis C virus and how it spreads in the community.

- 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 also use the blood collected for additional HIV testing.

- If the results of your second HIV test are inconclusive (if we still can't tell if you are infected or not), you will be referred for further testing and care.

- We will ask you if you have had any problems because you are a part of this screening.

- We will talk to you about HIV and other sexually transmitted diseases and give you information to help you protect yourself from getting them or passing them on to others.

- If you were asked to invite people you know to come for HIV testing, we will ask you questions about who you invited.

If you are HIV-uninfected: If your HIV test results determine that you aren't infected, we will give you information about how to prevent getting HIV.

If you are HIV-infected: If your HIV test results confirm that you are infected, we will check your viral load test to see if you might be eligible to participate in a study. If so, we may ask you if you are interested in participating in the study. The study is testing if case

manager support can help those who are HIV-infected. If you are not interested in this study, we will tell you where you can go to receive HIV care.

RISKS AND/OR DISCOMFORTS

Blood Draws

Taking blood samples may cause some pain, bruise your arm, or make you feel lightheaded. In rare cases you may faint. There is also a slight chance of infection when blood is drawn.

HIV Testing and Potential Social Harm

You may be nervous while you are waiting for your HIV test result. If the tests show that you have HIV, you may worry about your health and future. You will receive counseling before and after the test to help address your concerns. We will make every effort to protect your confidentiality during the study. However, it is possible that others may learn that you are part of this screening and they may think that you are infected with HIV or are at high risk for infection with HIV. Because of this you could have trouble finding or keeping a job. You could also have problems with your family, friends and community.

Sensitive Questions

The questions we will ask you about your sexual behavior and partners or about stigma you may have faced may make you feel uneasy. However, you do not have to answer any question that you do not want to and you can stop answering the questions at any time.

BENEFITS

We will test you for HIV, hepatitis C virus and syphilis. If you have any of these conditions we will help you receive care and treatment and tell you how to avoid passing them on to your sexual partners. The counseling you get during this study may help you avoid HIV and other sexually transmitted infections.

You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from these screening activities in the future. The information gathered during screening may help prevent HIV and other infections in the MSM community.

NEW INFORMATION

You will be told about any new information that might affect your willingness to take part in screening. You will also be told when the results of the research may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM SCREENING WITHOUT YOUR CONSENT

You may be withdrawn from screening without your consent if any of the following occur:

- You are unable or unwilling to follow all of the screening procedures or instructions.
- Screening is stopped or canceled.
- The study staff feels that participating in the screening activities would be harmful to you.

- You are not able to attend the screening visits or complete all of the screening procedures.

- Other reasons, as decided by the study staff.

ALTERNATIVES TO PARTICIPATION

You may choose not to participate in the study. [*Sites to include/amend the following if applicable:* You do not need to participate in the screening activities to be tested for HIV at our site. If you wish, we will tell you how to get HIV counseling and testing at other places.]

COSTS TO YOU

There will be no cost to you for any screening-related visits, laboratory tests or other procedures.

REIMBURSEMENT

You will receive [*site to add amount]* for your time, effort, and travel to and from the clinic for each scheduled screening visit. [*Sites to insert information about local reimbursement for the study.]*

CONFIDENTIALITY

All the information you give us as part of this study will be kept private. All your laboratory test results will also be kept private. You will get a unique study identification number that will be used instead of your name on your documents. However, at every screening visit we will ask you to identify yourself. This is to make sure that it is you who provides samples and information to us. Also we want to make sure that no other person than you can get your confidential laboratory test results. Only the study staff will be able to see records that identify you by name. This information will not be shared with others. All records will be stored in locked files at the study clinic. Results of your laboratory tests will be made available only to you when you visit the clinic. Your name will never be used in any publication or presentation about these screening activities.

[Sites to modify this suggested language as appropriate:] If you are under 18 years old, we [*must/do not need to*] inform your parents or guardian about the results of your HIV and syphilis tests, unless you would like us to tell them. If you are under 18 years old, we [*must/do not need to*] inform your parents or guardian about the results of your hepatitis C (HCV) test, unless you would like us to tell them. If [*we must / you choose to have us*] inform them of these test results, we will talk to you about the best way to inform them before we do so.

Your records may be reviewed by the sponsor of the study, the US National Institutes of Health (NIH) and their representatives, other government and regulatory authorities, *[insert name of site]* IRB/EC, study staff, study monitors and [*insert applicable local regulatory authorities*].

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the US Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US FDA. Even with

the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

A description of this study will be available on www.ClinicalTrials.gov. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

[Sites to include/amend the following if applicable:] In this study, you will be tested for HIV, hepatitis C virus and syphilis. [*Local/state/national*] regulations require study staff to report the names of people who test positive for [*HIV and other infections [sites should add that HCV and syphilis are reportable diseases if this is true for their location]*] to the [*local health authority*]. Outreach workers from the [*health authority*] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [*health authority*].

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of study participation. If you are injured, the [*institution*] will give you immediate necessary treatment for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries either through this institution or the US NIH. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about the screening activities, or if you have a research-related injury, you should contact [*insert name of the investigator or other study staff*] at [*insert telephone number and/or physical address*].

If you have questions about your rights as a research participant, you should contact [*insert name or title of person on the IRB or other organization appropriate for the site*] at [*insert physical address and telephone number*].

SIGNATURE PAGE

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

HPTN 078

Version 1.0
October 8, 2015
DAIDS Document ID: 11995

SCREENING INFORMED CONSENT FORM

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to complete the screening activities, please sign your name or make your mark below.

Participant Name (print)	Participant Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
Witness Name (print) (As appropriate)	Witness Signature and Date

SIGNATURE PAGE FOR PARTICIPANTS BELOW THE LEGAL AGE TO PROVIDE INDEPENDENT INFORMED CONSENT

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

HPTN 078

Version 1.0
October 8, 2015
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SCREENING INFORMED CONSENT FORM

Participant Assent

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to complete the screening activities, please sign your name or make your mark below.

Participant Name (print)	Participant Signature and Date

Parent/Legal Guardian Consent

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree for your child to complete the screening activities, please sign your name or make your mark below.

Parent/Guardian Name (print)	Parent/Guardian Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
Witness Name (print) (As appropriate)	Witness Signature and Date

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

HPTN 078

Version 1.0
October 8, 2015
DAIDS Document ID: 11995

ENROLLMENT INFORMED CONSENT FORM

Sponsored by: Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH).

PRINCIPAL INVESTIGATOR: *[Insert Name*]

PHONE: *[Insert Number]*

INTRODUCTION

You are being asked to take part in a research study that is designed to find out if support from a case manager can help HIV-infected people receive consistent HIV care and routinely take their HIV medication. Joining this study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason. This research study is for men who have sex with men (MSM) who have Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS.

Before you decided whether to join the study, we would like to explain the purpose of the study, the risks and benefits to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study you are being invited to join. Once you understand the study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

Before you learn about the study, it is important that you know the following:

- Your participation is voluntary. You do not have to take part in any of the tests, questionnaires or procedures in the study.
- You may decide not to take part in the study, or you may decide to leave the study at any time.
- If you decide not to take part in the study, you can still join another study at a later time if there is one available and you qualify.
- If you decide not to take part in the study, or decide to stop participating at any time, there will be no penalty or loss of the normal benefits provided to you at our clinic.

PURPOSE OF THE STUDY

The purpose of this study is to find out if support from a case manager can help HIV-infected people receive consistent HIV care and routinely take their HIV medication.

STUDY GROUPS

We plan to enroll 356 HIV-infected men and follow them for two years. Half of the participants will receive the intervention (support from a case manager [CM]) and the other half will not. At the end of the study, the two groups will be compared to see if the case manager support improved retention in care and medication adherence.

You will be "randomized" to either the group who will get case manager support or the group who will get the same care that patients normally get to stay in HIV care and take their HIV drugs properly. "Randomization" means that you are put into a group by chance. It is like flipping a coin. You have will an equal chance of being in either group. Both groups are important to the study.

CM Intervention Group

If you are in the CM intervention group, you will receive support from a case manager who will help you link to and stay in HIV care, and when the person is ready, start HIV medication and take it properly. The help from the case manager will be tailored to your needs.

Standard-of-Care (SOC) Control Group

If you are in the SOC control group, you will get the same care that patients normally get to stay in HIV care and take their HIV drugs properly.

Co-Enrollment in Other Studies

During the time when you are enrolled in this study, you may not enroll into other studies designed to help you link to HIV care or take your HIV medication properly.

STUDY PROCEDURES

If you decide to join the study, you will be asked to participate in 7 study visits over the course of two years. If you are in the CM intervention group (case manager group), you will also be contacted about the study on a monthly basis.

Enrollment Visit

Your enrollment visit will happen after you read, discuss, understand, and sign this form. We will help you understand the form and answer your questions before you sign this form. The procedures done at the Enrollment Visit will take about [*sites to fill in the amount of time*] hours.

During this visit:

- We will confirm where you live and how to contact you.
- We will ask you to give us permission to review your medical records.

- We will ask you to complete a questionnaire. This questionnaire will ask you about your use of recreational drugs and alcohol and your mental health.

- We will invite you to bring your sexual partner(s) for HIV testing. *[Note: Partner testing is conducted outside of the study and results are not recorded.]*

- If you are in the CM intervention group (case manager group), the study case manager will talk to you about HIV and give you information to help you decide where you would like to go for HIV care and when to start HIV drugs. You will decide how much support you need from the case manager. Communication between you and the case-manager can be by text, email, phone, or in-person. The session with the CM will be audio-recorded.

Monthly Contact

- If you are in the CM intervention group (case manager group), you will be contacted every month to confirm where you live and how to find you. We will ask if you are having any problems with your health or your HIV medication. We will ask you if you have had any problem because you are a part of this study. You may choose to have us call, email or text you every month. You can also ask to meet with the case manager on a monthly basis if you feel you need additional support.

Follow-up Visits

You will be asked to return to the clinic for a total of 5 Follow-up Visits. The procedures done at the Follow-up Visits will take about [*sites to fill in the amount of time*] hours.

During this visit:

- We will confirm where you live and how to contact you.

- We will ask you if you have had any problems because you are a part of this study.

- We will invite you to bring your sexual partner(s) for HIV testing.

- We will collect a small amount of blood (approximately 34 mL = about 7 teaspoons) to conduct CD4 cell count and viral load testing. Some of the blood will be stored for additional laboratory testing. These tests will give us information about the HIV virus and how the virus spreads in the community. The blood may also be used to test for the presence of HIV drugs and to learn more about how the body responds to HIV infection. If you have hepatitis C virus infection, the blood may also be used for testing to learn more about the hepatitis C virus and how it spreads in the community.

- If you are in the CM intervention group (case-manager group), you will meet with the case manager to talk about your HIV care and, if you have started taking it, your HIV medication. The case manager will help you with any problems you are having. The session with the CM will be audio-recorded.

Final Visit

At the end of two years, you will be asked to return to the clinic for a Final Visit. The procedures done at the Final Visit will take about *[sites to fill in the amount of time]* hours.

During this visit:

- We will confirm where you live and how to contact you.
- We will ask you to complete a questionnaire. This questionnaire will ask you about your sexual behavior and partners, medication adherence, health care use, use of recreational drugs and alcohol, your mental health and stigma you may have faced because you are an MSM.
- We will ask you if you have had any problems because you are a part of this study.
- We will invite you to bring your sexual partner(s) for HIV testing.
- We will ask you to participate in an exit interview where we will ask you about your experience of being in the study.
- We will collect a small amount of blood (approximately 40 mL = about 8 teaspoons) to conduct for CD4 cell count, HIV viral load and syphilis testing. Some of this blood will be stored for additional testing. These tests will give us information about the HIV virus and how the virus spreads in the community. The blood may also be used to test for the presence of HIV drugs and to learn more about how the body responds to HIV infection. If you have hepatitis C virus infection, the blood may also be used for testing to learn more about the hepatitis C virus and how it spreads in the community.
- We will contact you when the results of your syphilis test are available and, if your test is positive, we will ask you to return to the clinic one last time. If you have syphilis, we will refer you for care and treatment.
- If you are in the CM intervention group (case-manager group), you will meet with the case manager to talk about your HIV care and, if you have started taking it, your HIV medication. The case manager will help you with any problems you are having. The session with the CM will be audio-recorded.

If You Decide to Leave the Study Early

If you decide to leave the study early (before completing the final study visit), you will be asked to complete a final evaluation, which includes all of the procedures listed for the final visit.

When You Decide to Start HIV Drugs

If you decide to start taking HIV medication, we will ask your doctors for information about when you started these drugs and what your CD4 cell count and HIV viral load test results were at that time.

HIV Test Results for Your Sexual Partner

If your sexual partner is HIV-uninfected: If your sexual partner is found to be HIV negative at any study visit, we will give both of you information about how to prevent the spread of HIV.

If your sexual partner is HIV-infected: If your sexual partner is found to be HIV positive at any study visit, we will talk to him about what this test result means and where he can receive HIV care.

RISKS AND/OR DISCOMFORTS

Blood Draws

Taking blood samples may cause some pain, bruise your arm, or make you feel lightheaded. In rare cases you may faint. There is also a slight chance of infection when blood is drawn.

Sensitive Questions

The questions we will ask you about your sexual behavior and partners, recreational drug and alcohol use, your mental health or about stigma you may have faced may make you feel uneasy. However, you do not have to answer any question that you do not want to and you can stop answering the questions at any time.

Potential Social Harm

We will make every effort to protect your confidentiality during the study. However, it is possible that others may learn that you are part of the study and they may think that you are infected with HIV. Because of this you could have trouble finding or keeping a job. You could also have problems with your family, friends and community.

BENEFITS

The counseling you get during this study may help you avoid spreading HIV to anyone else. We will offer to test your sexual partner for HIV. We will test you for syphilis. If you have syphilis, we will refer you for care and treatment.

If you are in the CM intervention group, you will receive help from a case manager to stay in HIV care and take your HIV drugs properly.

You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from this study in the future. The information gathered during this study may help prevent HIV in the MSM community.

NEW INFORMATION

You will be told about any new information learned during this study that might affect your willingness to take part in the study. You will also be told when the results of the study may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be withdrawn from the study without your consent if any of the following occur:

- You are unable or unwilling to follow all of the study procedures or instructions.
- The study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.

- You are not able to attend clinic visits or complete all of the study procedures.
- Other reasons, as decided by the study staff.

ALTERNATIVES TO PARTICIPATION

You may choose not to participate in the study. [*Sites to include/amend the following if applicable:* There may be other studies going on here or in the community that you may be eligible for. Some of these studies may be able to help you stay in HIV care or take your HIV medication. If you wish, we will tell you about other studies that we know about.]

COSTS TO YOU

There will be no cost to you for any study-related visits, laboratory tests or other procedures.

REIMBURSEMENT

You will receive [*site to add amount]* for your time, effort, and travel to and from the clinic for each scheduled visit. [*Sites to insert information about local reimbursement for the study.]*

CONFIDENTIALITY

All the information you give us as part of this study will be kept private. All your laboratory test results will also be kept private. You will get a unique study identification number that will be used instead of your name on your documents. However, at every study visit we will ask you to identify yourself. This is to make sure that it is you who provides samples and information to us. Also we want to make sure that no other person than you can get your confidential laboratory test results. Only the study staff will be able to see records that identify you by name. This information will not be shared with others. All records will be stored in locked files at the study clinic. Results of your laboratory tests will be made available only to you when you visit the clinic. Your name will never be used in any publication or presentation about the study.

[Sites to modify this suggested language as appropriate:] If you are under 18 years old, we [*must/do not need to*] inform your parents or guardian about the results of your HIV and syphilis test, unless you would like us to tell them. If you are under 18 years old, we [*must/do not need to*] inform your parents or guardian about the results of your hepatitis C (HCV) test, unless you would like us to tell them. If [*we must / you choose to have us*] inform them of these test results, we will talk to you about the best way to inform them before we do so.

Your records may be reviewed by the sponsor of the study, the US National Institutes of Health (NIH) and their representatives, other government and regulatory authorities, *[insert name of site]* IRB/EC, study staff, study monitors and [*insert applicable local regulatory authorities*].

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the US Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US FDA. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

A description of this study will be available on www.ClinicalTrials.gov. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

[Sites to include/amend the following if applicable:] In this study, you will be tested for syphilis and your sexual partner may be tested for HIV. [*Local/state/national*] regulations require study staff to report the names of people who test positive for [*HIV and other infections*] to the [*local health authority*]. Outreach workers from the [*health authority*] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [*health authority*].

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of study participation. If you are injured, the [*institution*] will give you immediate necessary treatment for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries either through this institution or the US NIH. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about the study, or if you have a research-related injury, you should contact [*insert name of the investigator or other study staff*] at [*insert telephone number and/or physical address*].

If you have questions about your rights as a research participant, you should contact [*insert name or title of person on the IRB or other organization appropriate for the site*] at [*insert physical address and telephone number*].

SIGNATURE PAGE

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

HPTN 078

Version 1.0
October 8, 2015
DAIDS Document ID: 11995

ENROLLMENT INFORMED CONSENT FORM

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

_____	_____
Participant Name (print)	Participant Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date

SIGNATURE PAGE FOR PARTICIPANTS BELOW THE LEGAL AGE TO PROVIDE INDEPENDENT INFORMED CONSENT

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

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ENROLLMENT INFORMED CONSENT FORM

Participant Assent

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

Participant Name (print)	Participant Signature and Date

Parent/Legal Guardian Consent

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree for your child to join the study, please sign your name or make your mark below.

Parent/Guardian Name (print)	Parent/Guardian Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
Witness Name (print) (As appropriate)	Witness Signature and Date

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

HPTN 078

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SAMPLE STORAGE AND FUTURE USE CONSENT FORM

Sponsored by: Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH).

PRINCIPAL INVESTIGATOR: *[Insert Name*]

PHONE: *[Insert Number]*

POSSIBLE FUTURE TESTS

If you give permission, some of the plasma (a part of the blood) collected from you will be kept after the study ends for possible testing related to HIV and hepatitis C virus and to better understand laboratory tests related to this study. If you do not agree to have your left over plasma stored you can still be in this study. If you agree to store your plasma but change your mind later, you can contact study staff. We will then destroy your samples. If you agree, your left over plasma will be stored for at least three years after the study ends. Any future use, not related to HIV or hepatitis C virus, needs to be reviewed and approved by the NIH and local authorities. Your left over samples will not be sold or used for commercial reasons.

SIGNATURE PAGE

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SAMPLE STORAGE AND FUTURE USE CONSENT FORM

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agreed to join the study, please sign your name or make your mark below.

_____ My initials indicate that some of the plasma collected from me may be stored for future testing after study-related testing has been completed.

_____ I do not agree to allow left over plasma samples to be saved for long-term storage or future testing after study-related testing has been completed.

_____	_____	_____
Participant Name (print)	Participant Signature	Date

_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date

SIGNATURE PAGE FOR PARTICIPANTS BELOW THE LEGAL AGE TO PROVIDE INDEPENDENT INFORMED CONSENT

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SAMPLE STORAGE AND FUTURE USE CONSENT FORM

Participant Assent

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agreed to join the study, please sign your name or make your mark below.

_____ My initials indicate that some of the plasma collected from me may be stored for future testing after study-related testing has been completed.

_____ I do not agree to allow left over plasma samples to be saved for long-term storage or future testing after study-related testing has been completed.

_____	_____
Participant Name (print)	Participant Signature and Date

Parent/Legal Guardian Consent

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agreed for your child to join the study, please sign your name or make your mark below.

_____	_____
Parent/Guardian Name (print)	Parent/Guardian Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date

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

HPTN 078

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EXIT INTERVIEW CONSENT FORM

Sponsored by: Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH).

PRINCIPAL INVESTIGATOR: *[Insert Name*]

PHONE: *[Insert Number]*

INTRODUCTION

You are being asked to take part in a research study that is designed to find out if support from a case manager can help HIV-infected people receive consistent HIV care and routinely take their HIV medication. Joining this study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason. This research study is for men who have sex with men (MSM) who have Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS.

Before you decided whether to join the study, we would like to explain the purpose of the study, the risks and benefits to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study you are being invited to join. Once you understand the study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

Before you learn about the study, it is important that you know the following:

- Your participation is voluntary. You do not have to take part in any of the tests, questionnaires or procedures in the study.
- You may decide not to take part in the study, or you may decide to leave the study at any time.
- If you decide not to take part in the study, you can still join another study at a later time if there is one available and you qualify.
- If you decide not to take part in the exit interview, or decide to stop participating at any time, there will be no penalty or loss of normal benefits provided to you at our clinic.

PURPOSE OF THE STUDY

The purpose of this study is to find out if support from a case manager can help HIV-infected people receive consistent HIV care and routinely take their HIV medication.

STUDY PROCEDURES

If you decide to join the study, you will be asked to participate in an exit interview at the end of the study. This interview may include both a questionnaire to complete as well as a semi-structured interview (by talking to the interviewee). Both the questionnaire and the interview will ask you about your experience and opinions in administering the CM intervention in this study.

RISKS AND/OR DISCOMFORTS

Sensitive Questions

The questions we will ask you about your sexual behavior and partners, recreational drug and alcohol use, your mental health or about stigma you may have faced may make you feel uneasy. However, you do not have to answer any question that you do not want to and you can stop answering the questions at any time.

BENEFITS

You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from this study in the future. The information gathered during this study may help prevent HIV in the MSM community.

NEW INFORMATION

You will be told about any new information learned during this study that might affect your willingness to take part in the study. You will also be told when the results of the study may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be withdrawn from the study without your consent if any of the following occur:

- You are unable or unwilling to follow the study procedures or instructions.
- The study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- Other reasons, as decided by the study staff.

ALTERNATIVES TO PARTICIPATION

You may choose not to participate in the study. [*Sites to include/amend the following if applicable:* There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about.]

COSTS TO YOU

There will be no cost to you for this interview.

REIMBURSEMENT

You will receive [*site to add amount]* for your time and effort for this interview. [*Sites to insert information about local reimbursement for the study.]*

CONFIDENTIALITY

All the information you give us as part of this study will be kept private. All your laboratory test results will also be kept private. You will get a unique study identification number that will be used instead of your name on your documents. However, at every study visit we will ask you to identify yourself. This is to make sure that it is you who provides samples and information to us. Also we want to make sure that no other person than you can get your confidential laboratory test results. Only the study staff will be able to see records that identify you by name. This information will not be shared with others. All records will be stored in locked files at the study clinic. Results of your laboratory tests will be made available only to you when you visit the clinic. Your name will never be used in any publication or presentation about the study.

Your records may be reviewed by the sponsor of the study, the US National Institutes of Health (NIH) and their representatives, other government and regulatory authorities, *[insert name of site]* IRB/EC, study staff, study monitors and [*insert applicable local regulatory authorities*].

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the US Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US FDA. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

A description of this study will be available on www.ClinicalTrials.gov.. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of study participation. If you are injured, the [*institution*] will give you immediate necessary treatment for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries either through this institution or the US NIH. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about the study, or if you have a research-related injury, you should contact [*insert name of the investigator or other study staff*] at [*insert telephone number and/or physical address*].

If you have questions about your rights as a research participant, you should contact [*insert name or title of person on the IRB or other organization appropriate for the site*] at [*insert physical address and telephone number*].

SIGNATURE PAGE

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

HPTN 078

Version 1.0
October 8, 2015
DAIDS Document ID: 11995

EXIT INTERVIEW CONSENT FORM

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to participate in the exit interview, please sign your name or make your mark below.

Participant Name (print)	Participant Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
Witness Name (print) (As appropriate)	Witness Signature and Date

SIGNATURE PAGE FOR PARTICIPANTS BELOW THE LEGAL AGE TO PROVIDE INDEPENDENT INFORMED CONSENT

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Participant Assent

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to participate in the exit interview, please sign your name or make your mark below.

_____	_____
Participant Name (print)	Participant Signature and Date

Parent/Legal Guardian Consent

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agreed for your child to participate in the exit interview, please sign your name or make your mark below.

_____	_____
Parent/Guardian Name (print)	Parent/Guardian Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date

APPENDIX V

Tailored Case Management Intervention Components in At Risk US Populations (2005 – 2015)

HPTN 078 CM Intervention Component	First Author; Year; Location(s)	Design; Sample Size	Study Focus / Intervention Component(s)	Evidence of Effect	Cascade Component
My Life	Yehia; 2015; Philadelphia, PA[51]	Cross Sectional; Descriptive; 1359 newly HIV diagnosed adults	Testing location	- Testing/diagnosis locations without co-located outpatient care are associated with delayed linkage to care - Counseling and testing centers, correctional centers, and inpatient settings are found to delay linkage to care in comparison to medical clinics - Medical clinics integrate testing and medical services, facilitating linkage to care (decreased wait times, increased familiarity with facilities, supportive ancillary services)	- Linkage to care - Engagement in care
	Quinlivan; 2013; Chapel Hill, NC[49]	Qualitative; 30 HIV-positive women of color	Self determination theory in HIV	- Autonomy is lost at diagnosis due to stigma, feelings of helplessness, and lack of competency. Autonomy/self-motivation and competency should be regained to facilitate engagement in care - Welcoming environment at initial clinical encounter would influence support and self-motivation to return for following visits - Increasing health-related knowledge and healthcare navigation facilitates feelings of competency - Retention in care is influenced by strong relationships between providers and patients, but long-term engagement is most influenced by developing autonomy and self-management -	- Linkage to care - Retention in care - Self-management - Durability

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My Life (cont)	Hightow; 2011; Chapel Hill, NC[48]	Pre-post test; 81 HIV-positive MSM of color	Linkage to care program including: - Social marketing - Intense outreach - Medical/social support	- 76% viral suppression at 12 months - Odds of 1 clinic visit in 4 months post-intervention versus pre-intervention group (OR = 2.58; 95% CI 1.34 – 4.98) - Likelihood of clinic visit attendance decreased over time for both pre- and post-intervention groups, yet for the intervention group retention was significantly greater	- Linkage to care - Retention in care - Viral suppression - Durability
	Rajabiun; 2007; 6 cities from northwest, midwest, midatlantic and northeast regions [50]	Qualitative; purposive sampling; 76 HIV-positive adults; 26% MSM	Interviews to understand participants' experiences with engagement and retention	- Participants cycle in and out of care and this process is facilitated or obstructed by the relationship of the patient with the provider - Partnership, validation, trust, respect, and emotional intelligence were notable characteristics of providers who influenced patients to engage and remain in care - When patients felt that their provider was patronizing or that they encountered stigma, they were less likely to remain in care - Engagement depends upon: - Acceptance level of diagnosis - Ability to cope with substance abuse, mental illness and stigma - Healthcare provider relationships - External support systems - Ability to overcome practice barriers to care	- Linkage to care - Retention in care - Engagement in care - Inter-personal relationship building

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My Choices	Craw; 2010; Anniston, AL Atlanta, GA Baltimore, MD Baton Rouge, LA Chicago, IL Columbia, SC Jacksonville, FL Kansas City, MO Miami, FL Richmond, VA[53]	ARTAS II demonstration project; 626 HIV-positive adults	Strengths-Based Linkage Case Management; Identify barriers and solutions to overcome challenges to engagement in care	- 79% (497 of 626) of participants visited an HIV clinician at least once within the first 6 months - Number of case management sessions (2-5 sessions) was associated with greater linkage (OR = 2.95, 95% CI 1.88 – 4.62) - Mean time spent per client was 7.2; median 5.8 hours - Biggest barriers to engagement by patient self report were 1) feeling well; 2) lack of transport; 3) not ready to start HIV medications; 4) no insurance; 5) took too long to get an appointment - Durability of project was limited due to lack of funding - Those sites that continued the linkage program after funding ended had long-standing relationships with local health departments and a steady influx of HIV patients	- Linkage to care - Engagement in care
	Christopoulos; 2013; San Francisco, CA[52]	Qualitative; 34 HIV-positive adults; 55% MSM	Qualitative interviews around engagement and linkage in newly diagnosed	- Linkage to care experience lays groundwork for subsequent retention in care - All patients reported have to learn and manage the "administrative" aspects of care in order to stay engaged in care - Patient priorities change over time, often shifting from medical/physical concerns to psychological/social concerns – interventions must	- Linkage to care - Engagement in care - Retention in care

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				accommodate this shift in order to continue to engage patients in care	
My Care (Step 1)	Bradford; 2007; Portland, OR Seattle, WA Boston, MA Washington DC[27]	Prospective cohort; 437 HIV-positive adults	Health system and patient navigation through a "client navigator program"	- Relationship building noted in 86% - Navigation services were used in 74% - Participants who had improved engagement with their provider had "41% greater odds of undetectable viral load" and 32% "greater odds of reporting the optimal number of HIV visits at 12 months"	- Engagement in care - Retention in care - Viral suppression - Durability
	Willis; 2013; Washington DC[47]	Descriptive, observational; 5631 HIV-positive adults	Medical Case Management (MCM)	- 56.7% received care at MCM-funded facilities of which 76.2% (vs. 59.9% in non-MCM funded facilities) were retained in care, and 70.6% (vs. 75.7%) achieved viral suppression. - Those receiving care in MCM-funded facilities more likely to be retained in care (aOR 4.13; 95%CI: 1.93-8.85) and as likely (aOR 1.06; 95%CI: 0.68-1.62) to be virally suppressed. - Among 789 newly diagnosed persons, those diagnosed in MCM-funded facilities were not more likely to be linked to care within 3 months (aOR 0.50; 95%CI: 0.21-1.18).	- Linkage to care - Engagement in care - Retention in care - Viral suppression -

HPTN 078 CM Intervention Component	First Author; Year; Location(s)	Design; Sample Size	Study Focus / Intervention Component(s)	Evidence of Effect	Cascade Component
My Care (Step 2)	Naar-King; 2009; Detroit, MI[60]	Pilot randomized trial; 87 HIV-positive youth (16 – 29)	Motivational interviewing by peer versus professional	- Peer and professional interviewers had similar motivational interviewing scores - Established initial effect size for peer-based MI programs - Both groups improved the regularity of primary care HIV appointments - Peer outreach is a cost-effective and durable program	- Retention in care - Durability
	Hayley; 2014; New York City, NY Newark, NJ Washington DC Baltimore, MD Durham, NC Atlanta, GA[58]	Prospective, observational cohort; 2099 HIV-negative women at risk of HIV acquisition	Interpersonal relationship building; community engagement; reduction of external barriers; staff capacity building participant tracing	- Participant visit completion was 93% at 6 months - Participant visit completion was 94% at 12 months - Housing instability was a significant predictor of missed visits	- Engagement in care - Retention in care - Inter-personal relationship building - Durability
	Remien; 2005; New York City, NY[62]	Randomized controlled trial; 215 sero-discordant couples with suboptimal adherence	4 session, couple focused adherence to medication intervention	- Higher medication adherence post-intervention in proportion of prescribed doses taken (76% versus 60%) - Greater likelihood of high levels of adherence compared to controls - Effects diminish with time - No significance difference identified between increased adherence and viral suppression - Involvement of relationship partner in treatment decisions and adherence is durable, cost-effective and improves adherence and treatment support	- Engagement in care - Adherence - Retention in care - Durability

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My Care (Step 2) (cont)	Simoni; 2006; Multisite[32]	Meta analysis; 19 studies; 1839 HIV-positive participants; 53% MSM (median across all studies)	Randomized behavioral interventions in adults	- Behavioral interventions (e.g. education, cognitive behavioral therapy, motivational interviewing, group therapy, cue dosing) increased 95% adherence (OR = 1.50; 95% CI 1.16 – 1. n = 1633), but did not meet statistical significance for undetectable viral load (OR = 1.25; 95% CI 0.99 – 1.59; n = 1247) - In the sub-analysis that evaluated studies with 50% of greater MSM, the results for viral load were OR = 1.83; 95% CI 0.50 – 6.67)	- Adherence (self-report) - Viral suppression
	Nelsen; 2013; Houston, TX[61]	Cross-sectional survey; 244 HIV-positive adults	Patient intention to adhere to HIV treatment	- Intention to adhere (measured by the 13-item Intention to Adhere to HIV Treatment Scale) was the only "patient-centered" outcome that predicated adherence (OR 2.2; 95% CI 1.1 – 4.3)	- Adherence
	Holtzman; 2015; Philadelphia, PA[59]	Qualitative semi-structured interviews; 51 HIV-positive adults	Andersen's Behavioral Model	- Low retention and adherence was predicted by stigma, mental illness, substance abuse, low social support, poor reminder strategies, housing, insurance, symptoms, competing life activities, colocation of services, and provider factors - Barriers specific to retention included transportation, clinic experiences, and appointment scheduling - Barriers specific to adherence included medication characteristics, pharmacy services, health literacy, and health benefits	- Retention in care - Adherence

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My Health	Lewis; 2013; Midwest HIV Clinic[38]	Pre-experimental proof of concept study; 52 HIV-positive MSM	Pre-post test design; Tailored text messaging intervention	- Positive receptivity to text messages, both in content and frequency - Overall, participants had an improvement in viral load control (<75) and CD4 count - Decrease in number of missed medication days - Message fatigue was common but could be addressed through customizing and varying the messages delivered to make the intervention more durable	- Adherence - Self-management - Inter-personal relationship building - Viral suppression - Durability
	Schnall; 2015; New York City[57]	Focus Groups; 50 PLWH	mHealth technology	- Participants suggested several tools for meeting their healthcare needs, including: reminders/alerts, lab results tracking, and notes on health status. - mHealth technology can function as a social actor by providing chat boxes/forums, testimonials of lived experiences, and personal outreach. - Examples of media that can be used as a persuasive technology include games/virtual rewards, coding of health tasks, and simulations on how to interact and connect with others	- Adherence - Self management

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My Health (cont)	Hightow; 2011; Chapel Hill, NC; Bronx, NY; Chicago, IL; Detroit, MI; Houston, TX; Los Angeles, CA; Oakland, CA; Rochester, NY[55]	334 MSM of color	National HIV/AIDS Bureau program: Outreach, linkage, entry, and retention analysis	- Earlier linkage to care was significantly associated with the person who made the diagnosis also making the initial referral to care - Clinic appointment reminders, case finding for patients who had missed appointments, transportation assistance as well as dedicated providers were all factors that contributed to the high retention rate of 83% of participants at one year - Dedicated providers contributed to the sustainability of the program	- Linkage to care - Retention in care - Durability
	Gilman; 2012; five sites from the Northeast, Midwest, and the South[54]	Site visits; seven linkage programs in five sites	Hospital-based, integrated linkage to care programs	- Successful linkage programs are low cost, intensive, time limited, flexible, and unique - Successful programs directly employed linkage workers, actively referred newly diagnosed patients to medical care, employed person-centered case management, and were culturally and linguistically in concordance with populations served - Successful implementation of linkage programs requires coordination and integration of services among testing and treatment sites, sustaining funding sources, and ensuring commitment from program stakeholders and testing staff	- Linkage to care - Durability

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My Health (cont)	Maulsby; 2015; Chicago, IL; New York City, NY; Louisiana[56]	Descriptive; 2,615 HIV positive adults	Positive Charge HIV linkage and re-engagement in care program	- Through methods such as peer health navigation, peer-led group-based education, case management, and case finding 88% of participants were linked to care, 69% were retained in care and 46% were virally suppressed at follow-up - 90% of MSM in one site were engaged in care following enrollment - Sustainable programs targeting underserved populations are achievable	- Linkage to care - Retention in care - Engagement in care - Durability