Scaling up HPTN 074: a Cluster Randomized Implementation Trial of an Evidence-based Intervention for Antiretroviral Therapy for PWID in Vietnam

NCT number NCT03952520
Document Date 09/13/2022

SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

Scaling up HPTN 074: a Cluster Randomized Implementation Trial of an Evidence-based Intervention for Antiretroviral Therapy for PWID in Vietnam

Sponsored by:
US National Institute on Drug Abuse
US National Institutes of Health

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THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 3.0 /13 September 2022

Summary of revisions and rationales

Revisions have been made to update these changes **throughout the protocol.**

We are requesting to add a 3-question survey, the Provider REport of Sustainment Scale (PRESS), into the SNaP study. We plan to administer this scale to site staff (including counselors and navigators) who were involved with the delivery of SNaP 6-10 months following the completion of the SNaP study at each site. The purpose of the scale will be to assess the sustainment of the SNaP intervention at each of the sites, as well as characteristics of high and low sustaining sites. Study staff will contact site staff at the 42 HIV test sites that were involved in the SNaP study to invite them to participate in the survey. About 252 clinic staff (6 per site) will participate in the survey. Clinic staff who are interested in participating will be emailed electronic consents via a Qualtrics database to read and sign (if they choose to participate in the survey). They will then complete the fully self-administered survey on Qualtrics. The survey should take no more than 5 minutes to complete.

We are requesting to add qualitative interviews at 6-10 months post-endline into the SNaP study. We plan to conduct the interviews with clinic navigators/counselors (n=12) and site staff or site directors (n=24) from a sub-sample of 12 of the SNaP scale-up sites. Based on their scores on the Provider REport of Sustainment Scale, we will randomly select 6 “high sustainer” and 6 “low sustainer” clinics for these interviews. The purpose of these interviews is to understand how SNaP and SNaP implementation strategy adaptations influence normalization and sustainment of the SNaP intervention into HIV testing clinics after the removal of external study support. SNaP study staff will contact clinic navigators, site staff, and site directors and will invite them to participate in the interviews. All interviews will be conducted over Zoom in Vietnamese by bilingual Vietnamese research assistants trained in qualitative interviewing. Participants will provide informed consent before being interviewed. The interviews are expected to last approximately one hour. All interviews will be audio-recorded, transcribed verbatim, and translated to English.

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THE AMENDED PROTOCOL IS IDENTIFIED AS:
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Protocol
Version 2.0
13 September 2022

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List of abbreviations and acronyms

AE	Adverse event
ART	Antiretroviral therapy
CDC	Center for disease control and prevention
CFIR	Consolidated Framework
CFR	Code of Federal regulations
Co-I	Co-Investigator
DALY	Disability-adjusted life year
EBI	Evidence-based intervention
EC	Ethics committee
FDA	Food and drug administration
GNI	Gross national income
HIV	Human immunodeficiency virus
HMU	Hanoi Medical University
HPTN	HIV prevention trials network
ICH	International Conference on Harmonisation
IDI	In-depth interview
IGHID	Institute for global health and infectious diseases
IM	Intervention mapping
IRB	Institutional review board
JHU	John Hopkins University
MAT	Medication-assisted treatment
MID	Masked identification number
MMT	Methadone maintenance treatment
MoH	Ministry of Health
NGO	Non-governmental organization
NIDA	National institute on Drug Abuse
NIH	National Institute of Health
OHRP	Office for Human Research Protections
ORIC	Organizational readiness to change
OSU	Oregon State University
PC	Psychological counseling
PI	Principle Investigator
PID	Patient identification number
PWID	People who inject drugs
SA	Standard approach
SMC	Safety monitoring committee
SN	System navigation
SNaP	Systems navigation and psychosocial counseling
SoC	Standard of care
SOP	Standard operating procedure
TA	Tailored approach
TIM	Tailored intervention mapping
UNC	University of North Carolina
US	United States
VAAC	Vietnam Authority of AIDS Control

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SCHEMA

Purpose: To conduct a pragmatic implementation trial comparing two Intervention Mapping implementation approaches for scale-up of the evidence-based intervention (EBI), referred to as SNaP, in Vietnam, considering effectiveness, cost, and the characteristics of HIV test sites achieving successful or unsuccessful implementation. The two implementation approaches based on Intervention mapping, which are the one size fits all standard approach (SA) and the tailored approach (TA).

Design: This study is a cluster randomized, controlled implementation trial designed to assess two implementation approaches (standard and tailored) for scaling-up the SNaP intervention. The SNaP intervention combines systems navigation and psychosocial counseling for people who inject drugs (PWID), and it is designed to facilitate PWID's engagement in HIV and substance use care.

Study Population: The study population will consist of the following participant types, recruited from selected HIV test sites across Vietnam:

- ***PWID*** who present to the HIV test sites and test HIV-positive using the standard confirmatory HIV test
- ***HIV test site directors and staff***

Study Size: **PWID:** Approximately 6200 HIV-infected PWID will be recruited for medical record assessment at baseline; of those, a subsample cohort of 1500 PWID will be enrolled for detailed assessments at baseline, 12 and 24 months, including questionnaires and viral load determination.

HIV test site directors and staff: All site directors and staff at the 42 selected test sites, including the navigators and counselors in each site, will be recruited for the study.

Treatment Regimen: HIV test sites (n=42) will be randomized 1:1 to either:

- the one size fits all standard approach (SA); or
- the tailored approach (TA).

Study Duration: Study activities will span across 5 years, with approximately 27 months at each site and recruitment of PWID participants over 21 months. For PWID not in the subsample cohort, participation is a one-time visit. For the Subsample Cohort PWID or PWID selected for qualitative

	interviews, maximum study participation time is 24-27 months. For HIV test site directors and staff, maximum time in the study is 24-33 months.
Primary Objectives:	1) To compare the standard approach (SA) to tailored approach (TA) to scale-up an integrated intervention, SNaP, for PWID in HIV test sites in Vietnam. **(Aim 1)** 2) To measure the incremental costs of SA compared to TA for SNaP implementation in Vietnam. **(Aim 2)**
Secondary Objectives:	1) To explore the key characteristics of HIV test sites and clinics that successfully or unsuccessfully implement and sustain SNaP for each study arm. **(Aim 3)**
Study Sites:	42 HIV test sites across Vietnam

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OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME

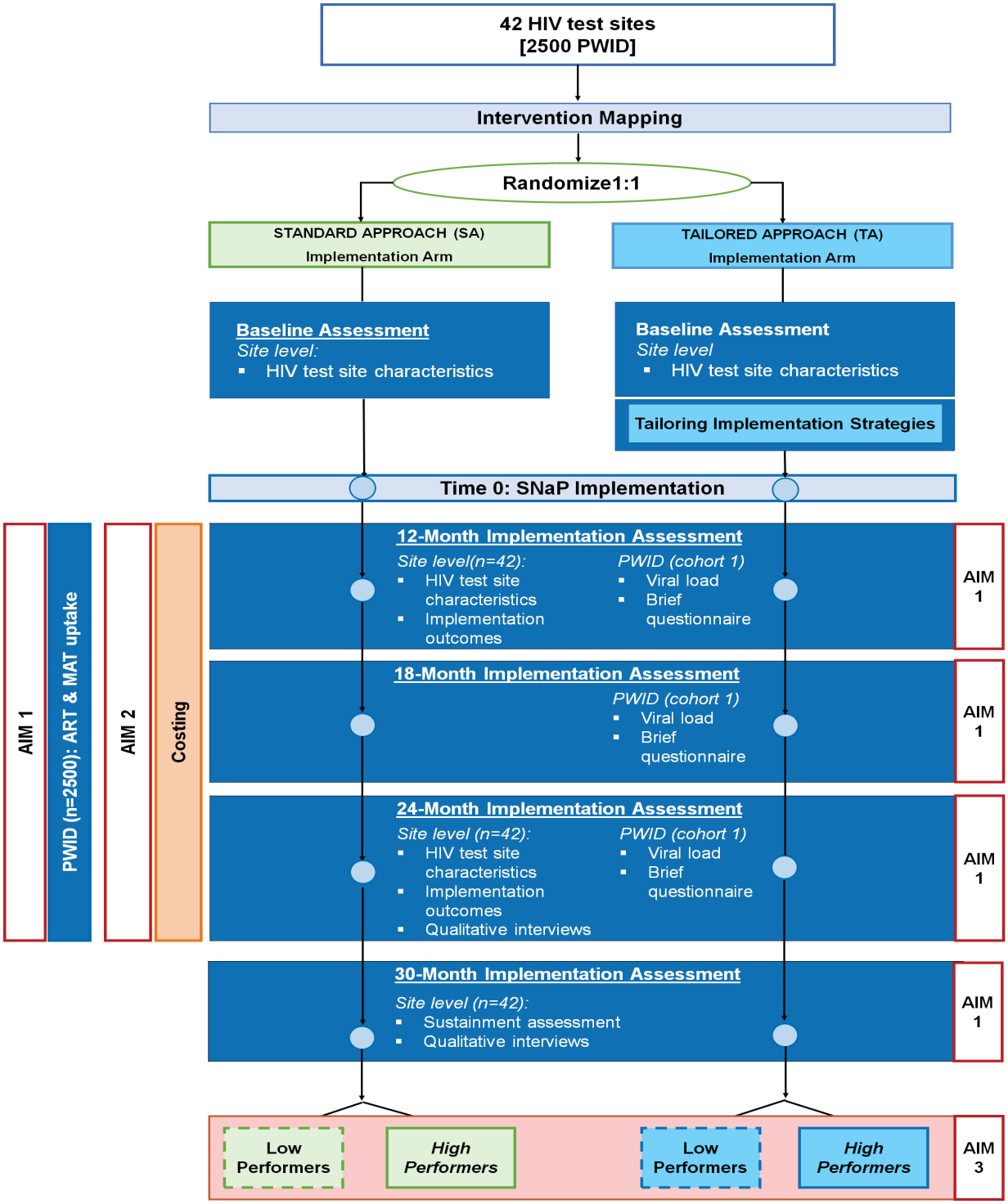


Figure 1: Study design overview and randomization scheme. Test sites are randomized 1:1 (21 sites per trial arm).

1. INTRODUCTION

1.1. Background

In early 2018, HIV Prevention Trials Network (HPTN) 074, a randomized, controlled, vanguard study for HIV-infected people who inject drugs (PWID), yielded exciting findings for HIV-infected PWID. Conducted in Vietnam, Indonesia, and Ukraine, HPTN 074 compared a systems navigation and psychosocial counseling integrated intervention (SNaP) to standard of care (SoC). SNaP, a scalable, flexible intervention, markedly increased antiretroviral (ART) use (**Figure 2**), viral suppression, and medication-assisted treatment (MAT) use, while also reducing mortality.[1] Transmission to HIV-uninfected partners also appeared to be reduced.

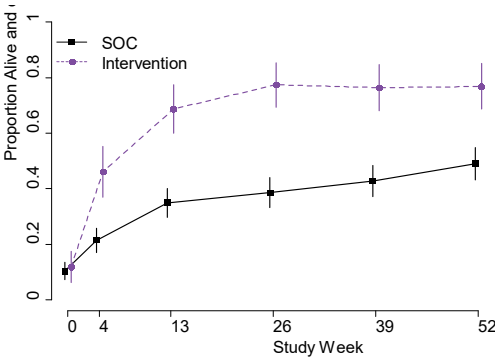


Figure 2: Proportion of HIV-infected PWID who were alive and self-reported ART use by week with 95% confidence intervals. Intervention = SNaP

The study population of HPTN 074 were actively injecting, HIV-infected PWID, ages 18-60 years with viral loads >1000 copies/mL (indexes) who were recruited and enrolled if they recruited an HIV-uninfected injection partner. Up to 5 injection partners could be enrolled per index.

Injection partnerships were randomized in a 3:1 ratio (standard of care (SoC) : SNaP) In the SNaP arm, HIV-infected indexes received an integrated intervention that included: 1) systems navigation to facilitate engagement, retention and adherence in HIV care and medication-assisted treatment (MAT, i.e. methadone in Vietnam), including negotiation of required laboratory testing, transportation, and ART initiation regardless of CD4+ cell count; and 2) psychosocial counseling using motivational interviewing, problem solving, skills building, and goal setting to facilitate initiation and adherence of ART and MAT. All navigator/counselors had addiction-related experience, but had a variety of education levels.

The effectiveness of SNaP was striking, but its effects were observed in a controlled trial environment. Many evidence-based interventions (EBI), such as SNaP, fail to fulfill their promise during implementation. Implementation may fail due to barriers that vary across target populations, providers, organizations and systems. Implementation of EBI is commonly one size fits all, with a Ministry of Health decreeing a nationwide, single implementation strategy. This approach was effective in bringing HIV counseling and testing and ART to many people, but some populations, such as PWID were left behind. To implement SNaP at scale, a one size fits all approach may suffice, but HIV test site-specific barriers may need to be addressed to reach this vulnerable population.

Intervention Mapping (IM), a multistep implementation process, incorporates theory, evidence, and stakeholder perspectives to ensure that intervention components effectively address key barriers to change. Intervention Mapping may improve centralized, one size fits all decision-making prior to implementation.

Intervention Mapping may also be extended to ***tailor*** implementation strategies to specific contexts using a multi-step process with initial development of a menu of implementation

strategies centrally, rapid assessment of local implementation barriers in each HIV test site, and selection of implementation strategies to match site-specific barriers.

In 2015, we collaborated with the Vietnam Administration for HIV/AIDS Control (VAAC) to identify implementation strategies to facilitate the MoH's plan to integrate MAT and HIV services.[2] Our approach comprised 3 steps: 1) 16 qualitative interviews with key stakeholders (MoH, clinic directors, staff) in Vietnam; 2) a matrix of facilitators and barriers to align potential implementation strategies; and 3) a poll with Vietnamese stakeholders and implementation science experts to select appropriate implementation strategies. Stakeholders noted patient benefits from integration, but clinic leaders and staff voiced concerns related to staff training and morale. We then designed an acceptable and feasible package of 3 implementation strategies: local champion, technical assistance, and audit and feedback, and presented it to the MoH as they rolled-out MAT/HIV integration. This approach was similar to IM, as it linked barriers and strategies using stakeholder feedback. Our use of the formal IM process in this study will ensure that these decisions are also strongly grounded in theory and empirical literature.

Standard Intervention Mapping may be sufficient to produce an appropriate national implementation package for the scale up of SNaP, but barriers at the local HIV test site-level may impede this approach. However**, a tailored approach addresses contextual needs and may improve scale up of EBI for PWIDs.** Unlike standard, MoH-decreed one size fits all approaches, tailored implementation allows for flexibility through a two-step local process: 1) rapid assessment of implementation barriers and facilitators in each site; and 2) selection of site-specific strategies using a pre-identified menu of potential strategies to address barriers.[3]

This study addresses priorities in the field of implementation science by: 1) using a rigorous method for selecting and tailoring implementation strategies,[2–4,6,7] 2) comparing a tailored approach to a standard multifaceted implementation strategy (rather than a more passive "straw man" strategy such as dissemination of educational materials or training alone),[4] and 3) assessing the incremental costs of a standard vs. tailored approach to implementation.[4]

1.2. Rationale

Despite decades of research and millions of dollars spent to develop EBI, PWID continue to bear a disproportionate HIV infection burden. This burden will only be reduced when EBI are effectively implemented at scale. But scale-up of any EBI, including SNaP, poses challenges that are often underestimated or not considered at all. Without effective implementation, SNaP will either languish with the other EBI that have never been implemented or fall short of its potential impact on the PWID epidemic because of poor implementation.

As mentioned, the SNaP intervention significantly increased ART use, viral suppression and medication-assisted use, and reduced mortality in Vietnam and Ukraine, two countries with very different health care systems. Barriers to implementing SNaP will vary by countries and health care systems. However, in this study, we are evaluating two approaches to selection of implementation strategies (Intervention Mapping vs. Tailored Intervention Mapping), not implementation strategies themselves, to address specific barriers.

Both Standard Approach (SA) and Tailored Approach (TA) are implementation approaches for identifying barriers and strategies to address those barriers that can be used in virtually any health care system. **This trial, comparing SA to TA, will allow us to identify appropriate implementation strategies for use globally, including cost and critical factors for**

success. This trial will allow us to determine which approach, SA or TA, is best to implement SNaP in terms of effectiveness, cost and the characteristics of HIV sites. This study will provide critical guidance to Ministries of Health worldwide regarding the most effective, cost-efficient approach to SNaP implementation. With this guidance, widespread implementation has the potential to significantly reduce mortality and improve health for HIV-infected PWID in resource-limited settings.

PWID need impactful interventions to reduce their HIV-associated morbidity and mortality and slow their HIV epidemic. SNaP provides such an opportunity. This implementation trial will provide critical guidance to policymakers worldwide who are charged with the task of reducing the burden of HIV infection among PWID. This guidance will accrue regardless of the trial outcome, based on the composite results of implementation outcomes, effectiveness outcomes, cost, and characterization of high and low performing test sites.

1.3. Theoretical Basis for the Implementation Trial

We will assess the effectiveness of two different approaches to implementation: 1) a "standard" multifaceted implementation approach (SA) and 2) a "tailored" approach to implementation (TA). Both will be based upon a rigorous approach to designing the implementation strategies called Intervention Mapping,[1] which is a systematic intervention development protocol that incorporates theory, evidence, and stakeholder perspectives to ensure that intervention components address key determinants of change.

Consistent with best practices in implementation science, our study is guided by theoretical frameworks to inform implementation processes (Intervention Mapping),[4] identify implementation barriers and facilitators (Consolidated Framework for Implementation Research; CFIR),[5] and assess implementation outcomes[6] (Proctor et al.'s implementation outcomes framework).[7] Intervention Mapping provides a methodological framework that will yield standard and tailored approaches to implementation. The CFIR is a comprehensive framework that identifies 39 factors that influence implementation outcomes. We will primarily focus on one of the five CFIR domains, the "inner setting," which will drive our assessment of HIV test site contextual factors that are likely to vary across sites. These factors include the age, maturity, and size of the test site; norms of the test site; organizational readiness to change; implementation leadership; and implementation climate. We posit that tailoring implementation strategies to address test site context will improve test site context and lead to better implementation and effectiveness outcomes. Proctor et al.'s framework also guides our assessment of key implementation outcomes: fidelity, penetration, acceptability, and cost.

As depicted in the conceptual framework (**Figure 3**), the effectiveness of SNaP scale-up will be determined by the implementation processes as operationalized through the SA and TA approaches. The two implementation approaches, SA and TA, must be implemented well (e.g. with fidelity), which in turn, affects SNaP implementation. Successful implementation of SNaP, with high fidelity, penetration and acceptability will lead to better effectiveness outcomes (ART uptake).

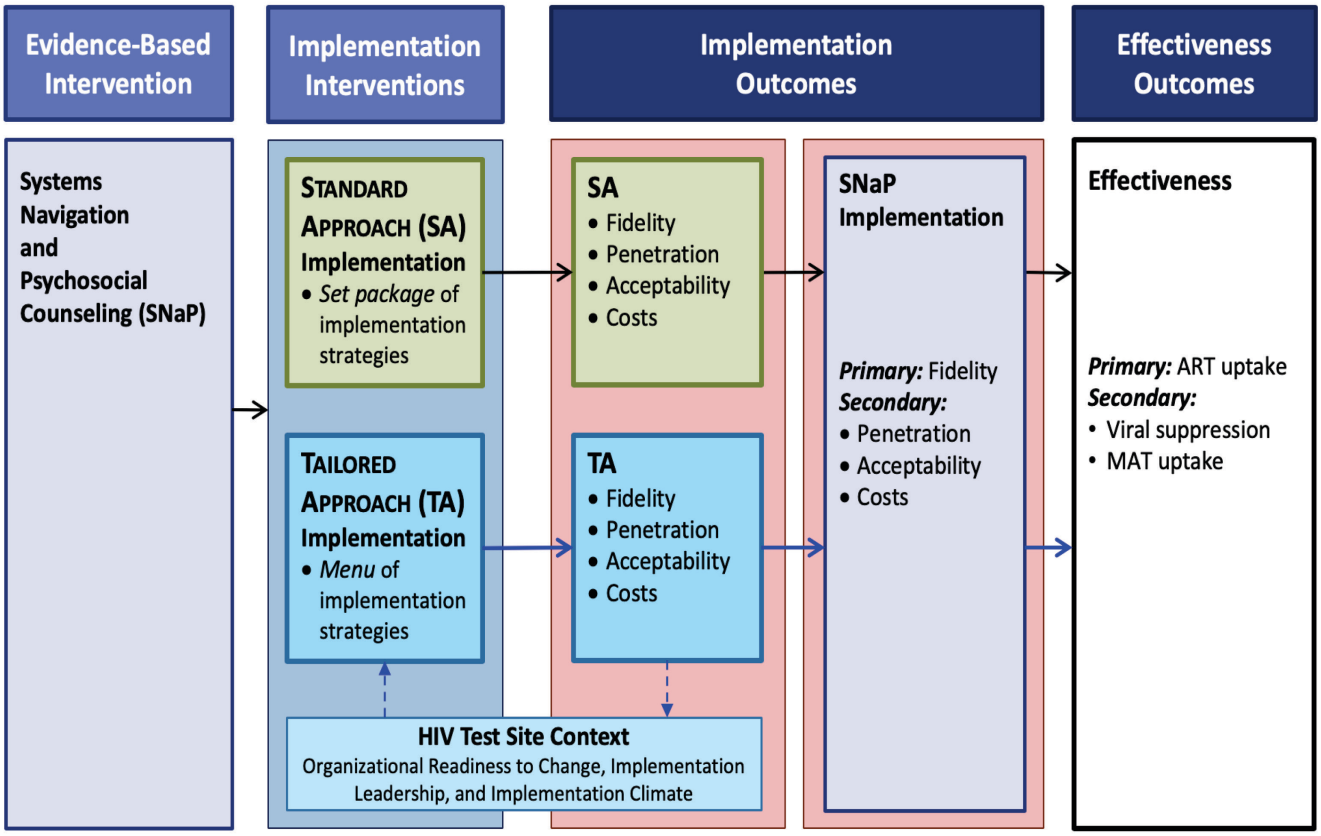


FIGURE 3. CONCEPTUAL FRAMEWORK

2. STUDY OBJECTIVES AND DESIGN

2.1. Study Objectives

The primary objectives of this study are:

1) **To compare the standard approach (SA) to tailored approach (TA) to scaling-up an integrated intervention, SNaP, for PWID in HIV test sites in Vietnam. (Aim 1)**

   We will conduct a two-arm, pragmatic cluster randomized implementation trial among HIV test sites in Vietnam. HIV test sites (n=42) will be randomized to receive one of two implementation approaches: a) SA—a standard, one size fits all multifaceted implementation package identified through Intervention Mapping, or b) TA—a tailored implementation package using Intervention Mapping with tailoring to each test site.
   - The primary outcomes are HIV test site-level EBI fidelity (implementation outcome) and ART uptake (effectiveness outcome).
   - Secondary implementation outcomes include penetration, acceptability, and cost.
   - Secondary effectiveness outcomes include viral suppression and MAT use.
   - We will conduct outcome assessments at 12 and 24 months.

2) **To measure the incremental costs of SA compared to TA for SNaP implementation in Vietnam. (Aim 2)**

Comprehensive costing of SA and TA will be performed using a micro-costing or "bottom-up" approach. This costing will include the intervention and the full implementation process, inclusive of Intervention Mapping and tailoring.

- The primary cost-effectiveness outcome will be the incremental cost-effectiveness ratio, expressed as the incremental cost per incremental ART uptake, comparing TA to SA.

The secondary objective of this study is:

1) **To explore the key characteristics of HIV testing sites and clinics that successfully or unsuccessfully implement SNaP for each study arm. (Aim 3)**

   We will use qualitative and quantitative site-level data collected at baseline and study completion to explore critical site characteristics, such as test site size, readiness to change, or implementation climate, of high and low performing sites. Test site-level success will be defined based on a high SNaP fidelity score and ART uptake exceeding 70% in newly diagnosed or previously diagnosed and not currently on ART HIV-infected PWID. We will also assess sustainment of the SNaP intervention at 6-10 months post-completion of 24 months at a given site.

2.2. Study Design

This study is a cluster randomized, implementation trial. The trial is designed to assess two implementation approaches (the one size fits all Intervention Mapping approach (SA) and the tailored approach (TA) for implementing SNaP, an evidence-based intervention (EBI). The SNaP intervention combines systems navigation and psychosocial counseling for people who inject drugs (PWID). The intervention is designed to facilitate PWID's engagement in HIV and substance use care.

The study is cluster randomized, and the unit of randomization is HIV test sites. These test sites will be randomized to receive either a standard approach (SA) procedure or a tailored approach (TA). The cluster sample size is 42 test sites with 1:1 allocation to each study arm.

3. STUDY SETTING AND POPULATION

3.1. Study Setting

The study will be conducted in 10 provinces in Vietnam. The provinces are located in the mountainous northern, northern delta, northern center, center and Cuu Long delta areas. In each of these areas, HIV test sites (n=42 sites) have been chosen based on a high prevalence of PWID in the area and in the specific test sites. The study will be performed in these test sites.

3.2. Study Population

3.2.1 PWID Participants:

PWID at the test sites will be enrolled with two levels of engagement for assessment of effectiveness outcomes (Aim 1):

1) For ART and MAT uptake outcomes, eligible participants will: test HIV-positive using the standard confirmatory HIV test in Vietnam; be 18 years or older; report a history of injection drug use in the past 6 months; and live in the HIV treatment catchment area.

   Only PWID, not all HIV-infected persons, will be offered SNaP at the selected HIV test sites. We conservatively estimate ~6200 eligible PWID over 21 months, after accounting for deaths. Most PWID will provide consent only for medical record assessment and will not be re-contacted.

2) For viral suppression, a subset of enrolled HIV-infected PWID will be selected and asked to additionally consent to re-contact. This subset (n=1500, target n=1200 with 20% loss to follow-up) will provide contact information and undergo an interview at baseline. This group will be re-contacted (see Sections 3.5.1 and 5.5 for retention strategy) for interview and assessment of viral suppression at 12 and 24 months after site implementation.

A sample of PWID (Sections 5.4, 5.5.1) will also be selected to participate in qualitative interviews after 24 months post-implementation, to assess high and low site performance characteristics (Aim 3).

Women are a minority of PWID and HIV-infected persons in Vietnam. We will engage women in the study in a proportion representative of the HIV-infected PWID population.

3.2.2 HIV Test Site Directors and Staff:

Site directors and staff will be considered study participants to assess implementation outcomes (Aim 1), costs (Aim 2), and high and low site performance characteristics (Aim 3). Eligible participants will include all site directors and staff at test sites including the navigators and counselors in each site. All site directors and staff will provide informed consent.

3.3. Inclusion Criteria

PWID participants:

1) HIV infection:
   - Newly diagnosed HIV infection, based on confirmatory test at the test site, and not currently on ART at the time of the study; ***or***
   - If previously diagnosed with HIV infection, then not currently on ART at the time of study enrollment (self-reported)
2) Age 18 years or older
3) Injection drug use within the past 6 months (self-reported at time of screening)
4) Willingness to provide informed consent

Site directors and staff:

1) All site directors and staff, including the navigators and counselors, at the selected HIV test sites
2) Willingness to provide informed consent

3.4. Exclusion Criteria

PWID participants:

1) Residence outside of the catchment area of local antiretroviral therapy (ART) and medication-assisted treatment (MAT, e.g. methadone) clinics
2) Currently on ART at time of study enrollment (self-reported)
3) Planning to move out of the catchment area within the next 24 months.

3.5. Recruitment Process

The study population comprises HIV-infected PWID not on ART and HIV test site directors and staff.

HIV-infected PWID participants will be either newly-diagnosed HIV infected or previously diagnosed HIV-infected who are not on ART. PWID participants will provide consent for medical record review. A subset of enrolled PWID will also be consented to allow re-contact at a later date. This subset will be re-contacted for collection of a dried blood spot for viral suppression and a brief questionnaire at baseline, 12, 18 and 24 months.

Test site directors and staff will undergo interviews for measurement of implementation-related outcomes.

3.5.1 Persons who inject drugs (PWID)

All persons meeting the eligibility criteria presenting to 42 HIV test sites in Vietnam will be approached for inclusion in the study. Recruitment will immediately follow routine post-test counseling procedures. Eligible persons will be informed of the study and consent will be requested to access their medical records at local HIV and methadone clinics. In addition, consent will be requested for audio-recording of psychosocial counseling sessions. Retention for the primary study participants is not required, as the only follow-up is through medical record review.

In a subset of the primary study participants (n=1500), we will also obtain consent for re-contact at a later date. These participants will be contacted by telephone and undergo a brief interview. Retention will be facilitated by quarterly contact by telephone to ensure that the number has not changed. If we are unable to reach a participant, we will contact a family member or friend, using a contact number provided during the original consent process.

The expected overall number of PWID is ~335 per month for 21 months or 7035. After accounting for approximately 12% mortality, as seen in a previous study, the expected number of PWID for outcome measurement is ~6200.

We will enroll a subsample cohort of 1500 PWID to obtain a sample of 1200 PWID for detailed assessments, including questionnaires and viral load determination. We recruit all eligible PWID into this subsample cohort, until we reach the 1500 sample size. **The 1500 allows for a 20% loss to follow-up (evaluable n=1200).**

3.5.2 Site staff & site directors

All HIV test site staff, including site directors, will be recruited for participation in this implementation science study. The study will be explained by the Vietnam Administration for HIV/AIDS Control (VAAC) representatives to the site directors. Consent will be obtained from all test site staff prior to data collection procedures.

3.6. Co-Enrollment Guidelines

Participants should not be currently participating in any other HIV study.

3.7. Participant Retention

3.7.1 Persons Who Inject Drugs (PWID)

Retention for the primary PWID study participants is not required, as the only follow-up is through medical record review.

In a subset of the primary study participants (n=1500), retention will be facilitated by quarterly contact by telephone to ensure that the number has not changed. If we are unable to reach a participant, we will contact a family member or friend, using a contact number provided during the original consent process.

3.8. Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. The investigators may also withdraw participants from the study in order to protect the participant's safety.

Participants may also be withdrawn from the study if the study sponsor, UNC or local IRBs or the SMC terminate the study prior to study completion.

Participants will be considered terminated from the study if the participant actively withdraws or dies during the course of the study.

4. STUDY INTERVENTION AND IMPLEMENTATION PACKAGES

4.1. Evidence-based Intervention: Systems Navigation and Psychosocial Counseling (SNaP)

PWID with confirmed HIV infection at the test site will receive the SNaP integrated intervention that includes: 1) systems navigation to facilitate engagement and retention in HIV care and MAT (currently methadone in Vietnam), and to negotiate required laboratory tests (e.g. CD4 counts) or transportation; and 2) psychosocial counseling using motivational interviewing, problem solving, skills building, and goal setting to facilitate ART and MAT initiation and adherence.

As an implementation study, navigators/counselors will not be compensated by the study.

Systems navigators will initially meet participants twice, in-person or by telephone, within 8 weeks of enrollment. Subsequent sessions, based on participants' needs, will be conducted in-person, by telephone, or SMS text.

Psychosocial counselors will provide participants with a minimum of one counseling session within 4 weeks of enrollment. The session will focus primarily on ART initiation, ART adherence and MAT. To determine the need for additional sessions, the counselor will use a standardized inventory to assess the participants' need for counseling on risk reduction, drug treatment entry and retention, HIV medical care, ART and MAT adherence, depression, alcohol dependence, and social support. Counseling session content will be incorporated in a manual, similar to that used in HPTN 074, which will be used by the counselors to ensure coverage of key topics and specific psychosocial counseling techniques. Participants will be offered the opportunity for additional booster sessions, if needed, at ~1 and 3 months after enrollment. Participants who have not initiated ART, have low levels of adherence to ART, or have not begun MAT will be able to receive additional counseling sessions through self-referral or referral by the systems navigators.

We will train existing HIV test site staff, selected by test site directors, to become systems navigators and psychosocial counselors for SNaP.

4.2. Implementation Packages

Overview:
Maximizing the public health impact of EBI requires the judicious use of implementation strategies, defined as "methods or techniques used to enhance the adoption, implementation, and sustainment of a clinical program or practice."[8] Over 70 discrete implementation strategies (e.g., audit and feedback, supervision, opinion leaders) have been identified,[9,10] but specific strategies must be matched to the EBI.[11]

Effective implementation typically requires selection of multiple discrete strategies to address multilevel determinants (barriers and facilitators).[12-14] Tailoring implementation strategies to address context-specific barriers may be more effective than one size fits all approaches.[15] In this study, we will use a systematic intervention development protocol, Intervention Mapping,[4] to develop *both* standard and tailored implementation strategies. IM is a multistep process that is inherently ecological and incorporates theory, evidence, and stakeholder perspectives to ensure that intervention components effectively address key barriers to change.

Description of Intervention Mapping:
Intervention Mapping is one of the most rigorous and relevant approaches to designing implementation strategies.[2,3] It will be used to identify a core set of discrete strategies for the standard condition and that may be used for the tailored condition. We believe that the standard multifaceted strategy will address the primary barriers faced by the majority of clinics. However, there is evidence that implementation strategies may be more effective if they are tailored to specific contexts,[4] and emerging perspectives on tailoring suggest that barriers may need to be assessed and addressed in an iterative fashion throughout the process of implementation.[5] Thus, while clinics in the tailored condition will have access to the multifaceted implementation strategy developed for the standard condition, it will differ in several important ways.

First, the tailored condition will also have access to an additional menu of implementation strategies derived from the Intervention Mapping process that will be connected to potential site-

specific barriers. Second, they will receive three 1-hour coaching sessions with the central implementation team that will focus on identifying and prioritizing site-specific barriers and identifying theory and evidence-based implementation strategies to address them. Third, the tailoring approach will be dynamic in that monthly calls with the central implementation team will afford the opportunity to identify new barriers and strategies throughout all phases of implementation.

The tailored strategies that each clinic deploys may be less intensive than the "standard" condition if they have strong infrastructure and implementation support already in place, or more intensive if numerous site-specific barriers need to be addressed. We believe that both the standard and tailored conditions will be effective in improving implementation and clinical outcomes, but that the tailored condition will outperform the standard condition as it more appropriately addresses site-specific needs.

Central Implementation Teams:
A central implementation team will be used to conduct the Intervention Mapping that occurs *prior to* randomization (Figure 1).

After randomization, two central implementation teams (one for each arm) will facilitate study implementation. Implementation will be done for both arms simultaneously in a rolling process, working systematically through the regions of Vietnam.

Central implementation teams will have separate group calls with the SA and TA test sites every 6 months to share experiences and lessons learned.

Each central implementation team will comprise:

1) A UNC-Vietnam Hanoi staff member,
2) A VAAC representative, and
3) A Hanoi Medical University (HMU) representative.

Summary of SA and TA Procedures:
Prior to randomization (see **Figure 1**), standard intervention mapping approach (SA) arm will be conducted at the **central level**, by our study's IM central implementation team, for all 42 sites. As the SA will be conducted at the central level (i.e., not site-level), it will not be specific to a particular site. The SA will be applied to all 42 sites as the standard implementation package. Then, after randomization, the 21 sites randomized to the Tailored Approach (TA) arm will receive additional ***tailored*** Intervention Mapping. The TA central implementation teams will conduct tailored Intervention Mapping at each TA site, tailoring the implementation strategies to fit each TA site specifically.

4.2.1 Standard Implementation Package:

Intervention Mapping (SA arm):

In Year 1, during the Pre-implementation Phase of this study (see Section 5.1), the central implementation team will engage our local partners to accomplish the following steps of Intervention Mapping:

Step 1: Conduct a needs assessment to identify determinants (barriers and facilitators) of implementation. The needs assessment will draw upon data from HPTN 074, which included qualitative interviews with navigators, counselors,

clinic directors, and PWID on their experiences with SNaP and surveys among PWID on acceptability of SNaP. We will partner with our OAB and the VAAC to identify additional determinants

Step 2: State outcomes (e.g., *implementation outcomes* such as fidelity, penetration, acceptability, and costs; *effectiveness outcomes* such as ART uptake, viral suppression, and MAT uptake) and performance objectives (e.g., *who* needs to do *what* to implement and sustain SNaP).

Step 3: Create matrices that relate determinants (Step 1) to performance objectives (Step 2), and list specific change objectives that will serve as "targets" that need to be addressed by theory and evidence-based implementation strategies.

Step 4: Identify appropriate implementation strategies. This step will draw upon previously published compilations of implementation strategies, as well as behavior change techniques and methods that are useful in specifying the theoretical mechanisms by which these strategies may exert their effects.

Based upon our preliminary work from HPTN 074, we anticipate that the implementation strategy will include opinion leader, leadership buy-in, and external technical assistance, but additional strategies will undoubtedly emerge during Intervention Mapping. The protocol for this strategy will be formalized for use in both SA and TA arms.

The *initial Intervention Mapping process will yield a multifaceted implementation strategy that we believe will be feasible for national scale-up (SA condition).* It will also yield *a more extensive list of implementation strategies that can be used by HIV test sites to address site-specific barriers in the TA condition.*

4.2.2 Tailored Implementation Package:

Tailored Approach (TA): Intervention Mapping + tailoring (TA)

In addition to having access to the standard implementation package, TA sites will have access to a broader menu consisting of 4-6 strategies identified through the Intervention Mapping process. Participating agencies (provincial health officials, HIV test sites) in TA will receive resources and coaching to assist them in tailoring their implementation strategy to address key determinants of change throughout the implementation process. Consistent with our guiding determinant framework[8] (CFIR[9]), we will assess inner setting factors that may influence implementation processes, including: organizational readiness to change, implementation leadership, and implementation climate, and available resources.

We will conduct this assessment using a structured form to be completed by each of the 21 clinics in the TA arm electronically, prior to implementation. These assessments will suggest site-specific targets for change that could be addressed through tailored implementation strategies.

Each TA site will also receive three 1-hour coaching sessions from the central TA implementation team via video-conference. These calls will address additional site-specific barriers to implementation through a structured brainstorming process,[16]

prioritizing barriers that are most important and modifiable, and selecting theory and evidence-based strategies from the Intervention Mapping-based menu that address them. Some test sites will need to engage in strategies in addition to the standard implementation package to address site-specific needs. However, some sites may not need to use all strategies outlined in the standard IM implementation package. For example, if a test site already has strong supportive leadership in place, it may not need to use the leadership buy-in activities.

A central TA implementation team will have monthly calls with local implementation teams to monitor each TA site. Calls will focus on site-specific challenges and assess ongoing implementation. If adjustment is needed, site-specific standard operating procedures (SOP) will be updated by the site and reviewed centrally, and the central TA implementation team will re-train TA site implementation staff by video-conference.

5. STUDY PROCEDURES

An overview of study visits and procedures is presented below. Summaries of the participant schedules of visit procedures are presented in **Appendices I, II, and III**. Detailed instructions to guide and standardize study procedures across test sites will be provided in the SOPs. The UNC and UNC-Vietnam staff are responsible for developing all SOPs.

5.1. Pre-implementation Study Procedures

In Year 1, pre-implementation activities will include:

1) Develop assessment instruments and SOPs
2) Meet with provincial leaders
3) Conduct Intervention Mapping
4) Randomize test sites
5) Conduct baseline assessment of site context
6) Trainings:
    - Train navigators and counselors
    - Train on seek strategies
    - Train on implementation strategies

5.1.1 Developing assessment instruments and SOPs

Our study investigators and UNC staff will develop assessment instruments for the baseline assessments and trial, and UNC and UNC-Vietnam staff will develop SOPs for the study.

5.1.2 Meetings with provincial leaders

Our centralized implementation team comprised of UNC-Vietnam, VAAC, and HMU staff will meet with each provincial AIDS committee in the study provinces to disseminate HPTN 074 findings and introduce SNaP, SA and TA processes, and the cluster randomized implementation trial.

5.1.3 Intervention Mapping

Prior to randomization and baseline assessment, we will apply Intervention Mapping to systematically identify implementation strategies for the SA arm and the menu of

implementation strategies for the TA arm. See **Section 4.2.1** for detailed Intervention Mapping steps to be conducted in Year 1.

5.1.4 Randomization

We obtained a complete list of the 136 HIV test sites in Vietnam, including the number of persons tested per month, positivity rates, and proportion of PWID. These data have been used to identify 42 proposed test sites for inclusion in this implementation study.

Test sites will be stratified by region and size, then randomized to either arm at a 1:1 ratio (21 sites per trial arm). Randomization will be blocked within strata to ensure equal distribution by arm.

5.1.5 Baseline assessment of site context (see also Section 7.1)

After randomization and prior to SNaP intervention implementation (Figure 1), we will ask each of the 42 test sites to complete a survey assessing the following baseline measurements at each site:

Site demographic characteristics (in the past 12 month):

- Number of HIV tests performed
- PWID size (number of HIV tests performed who are PWID)
- PWID proportion (number of PWID over total tests performed)
- Sex distribution (men and women who are PWID)
- Staff information
- Current support from Non-governmental organizations (NGOs)

Baseline test site context measurements (see **Table 1** for details):

- Organizational readiness to change
- Implementation leadership
- Implementation climate

Sites will be asked to complete a Qualtrics survey assessing each of these measurements and return it within 1 week.

Table 1. Test site context measures

Test site context measure	Definition	Measure or Scale*
Organizational readiness to change	Organizational members' shared resolve to implement change and shared belief in collective capability to do so.	ORIC: 12-item scale used to measure readiness for implementation.[17]
Implementation leadership	Degree to which a leader is proactive, knowledgeable, supportive in evidence-based practice implementation.	Implementation Leadership Scale (ILS): 12-item scale with 3 items measuring each of the 4 dimensions.[18]
Implementation climate	The extent to which organizational members perceive that innovation use is expected, supported and rewarded.[19]	Implementation Climate Scale 6-item scale measuring expectations, support & rewards.[20]

The assessments of the 21 TA sites will be used to tailor and finalize implementation packages for each TA site (see **Section 4.2.2**).

5.1.6 Trainings

- *Selection and training of navigators and counselors:*

We will train existing HIV test site staff, selected by test site directors, to become systems navigators and psychosocial counselors for SNaP. Test sites will nominate up to three staff per test site as systems navigators and/or counselors. Similar to HPTN 074, the roles of navigators and counselors may be performed by a single person or two distinct persons at the discretion of the test site.

We will conduct regional (north, south, central) trainings for navigators and counselors for all study test sites to ensure that SNaP training is uniform across study arms *prior to* notifying the sites of their SA/TA allocation.

The 2-day, in-person training will be conducted by the centralized training team and rely heavily on the training manual developed for HPTN 074, which will be minimally modified for use at scale. The training will include introduction to motivational interviewing, counseling techniques practices, and a series of guided role play activities, in which real-time feedback will be provided by the training team. Any new navigators or counselors will be trained similarly. Refresher trainings will be held annually.

- *Training on seek strategies:*
  At the regional training, implementation teams will provide strategies to reach out to PWID in their catchment area. Strategies will include communicating with needle exchange sites, MAT clinics and other substance use treatment centers (including mandatory 06/07 detoxification centers). The goal is to ensure active referrals of MAT patients to HIV test sites and provide information cards about HIV testing to PWID to distribute in their networks. These strategies were used to effectively "seek" PWID in HPTN 074.

- *Training on implementation strategies for SA and TA:*
  During or immediately after the navigator/counselor regional training, a 2-day regional training will be held for all test sites to introduce the project, orient to common implementation barriers and facilitators across sites, and train teams on the SA implementation package. TA implementation teams will subsequently visit each TA site in the region to conduct trainings on site-specific implementation strategies.

5.2. Cluster Randomized Implementation Trial Initiation (Aim 1)

After training completion, sites will implement the SNaP intervention and initiate the trial (Time 0 in Figure 1). SNaP will be implemented as the study rolls out. Specifically, upon trial initiation, trained navigators and counselors will provide SNAP to all accepting PWID testing positive for HIV at the test sites. Time 0 for each site will be the first day that the SNaP intervention is offered at that site.

Each site will consent PWID with a positive confirmatory test at the post-test counseling visit who are willing to allow medical chart review at MAT and ART clinics. Injecting drug use information is collected as part of routine protocol at HIV test sites and will be used to identify eligible participants for the study.

5.2.1 Central Implementation Teams (see also Section 4.2)

As stated in Section 4.2, distinct central implementation teams (one for each arm) will facilitate study implementation. Each implementation team will comprise:

1) A UNC-Vietnam Hanoi staff member,
2) A VAAC representative, and
3) An HMU representative.

Implementation will be done for both arms simultaneously in a rolling process, working systematically through the regions of Vietnam. Central implementation teams will have separate group calls with the SA and TA test sites every 6 months to share experiences and lessons learned.

5.3. Cost-effectiveness Data (Aim 2)

Measurements: Based on our prior experience with costing behavioral interventions to reduce hazardous alcohol use in Vietnam we will conduct an empirical costing study of SNaP—including SA and TA and the actual process of implementation itself—from a societal perspective.

We will estimate implementation costs prospectively by:
- Embedding a trained costing specialist within each central implementation team (one per arm),
- Documenting all resources used (e.g., staff training level and time, travel costs, supplies, etc.) and
- Estimating the unit cost of each resource.

To estimate the unit health system cost of each intervention, we will perform detailed budgetary analysis including:
- Interviews of key staff,
- Review of logbooks/timesheets, and
- Time-and-motion studies to record navigator, counselor, and other staff time devoted to various activities on ≥15 randomly selected days,
    - This will be conducted by the costing specialists, in each of 12 clinic sites (6 sites per arm, selected purposively to provide representation of patient volume, urban/rural status, and geography) over the course of the trial.

To estimate patient costs, we will:
- Administer a survey to a smaller subset of the 1500 PWID subsample cohort at baseline and at a single follow up visit of 12 or 18 or 24 months (depending on enrollment time of PWID participants)- to collect data on direct and indirect (lost wages, child care, etc.) costs of clinic visits and other elements (e.g., medication side effects) associated with ART, MAT, and SNaP itself. We will randomly sample up to 420 PWID participants among the 1500 PWID subsample cohort to administer this survey.

Cost data collection will be based on the Tool to Estimate Patient Costs, which we have adapted and used in Uganda.[21]

5.4. Procedures to Identify and Characterize High and Low Performing and Sustaining Sites (Aim 3)

We will identify high and low performing sites in both study arms based on SNaP fidelity and

ART uptake targets for PWID clients. We will assess these characteristics qualitatively and quantitatively.

To assess characteristics of high and low performing sites in depth, we will conduct qualitative interviews with:

- HIV-infected PWID, including those that received SNaP and those that declined,
- systems navigators and psychosocial counselors, clinic staff, and clinic directors in both SA and TA arms.
- Health providers and/or adherence counselors at HIV outpatient clinics near these test sites in both SA and TA arms

We will also assess the characteristics of high and low performing sites based on quantitative characteristics derived from the implementation outcomes, test site demographics, and test site context.

To assess characteristics of high and low sustaining sites in depth, we will conduct qualitative interviews with:

- Systems navigators and psychosocial counselors, clinic staff, and clinic directors in both SA and TA arms.

We will also assess the characteristics of high and low sustaining sites based on quantitative characteristics derived from the implementation outcomes, test site demographics, and test site context.

Our *a priori* definition of successful implementation at 24 months is:

- A site with a fidelity score of 136 (see Section 7.2) and 70% ART uptake among its newly diagnosed or previously diagnosed and not currently on ART PWID clients.

The fidelity score and ART uptake are based on the Vietnam site's experience in HPTN 074. In the SNaP arm of HPTN 074, 72% of PWID were using ART at 12 months; in Vietnam, 88% of PWID were using ART at 12 months. Based on these results, 70% is a reasonable target for this implementation trial. We will consider any person lost to follow up as having failed ART use and not virally suppressed.

5.4.1 High and Low Performing and Sustaining Sites Data Collection:

In-depth interviews - PWID at high and low performing sites: We will conduct six semi-structured in-depth interviews (IDIs) with PWID in each of three sites of the following four site performance types (12 test sites; 72 interviews): 1) SA low performers; 2) SA high performers; 3) TA low performers; and 4) TA high performers. Three PWID will have participated in SNaP and three PWID will have declined SNaP. We will ask participants about barriers and facilitators to uptake of ART and MAT and ART adherence, attitudes and experiences in the HIV test site, with test site staff, and if appropriate, with navigators and counselors.

In-depth interviews - navigators and counselors, clinic staff, and clinic directors: In these same 12 test sites, we will conduct semi-structured IDIs with navigators/counselors (n=12-24), site staff (n=12), site directors (n=12) and HIV providers (n=12) to inform the context and processes that may underlie SNaP success and failures (total n=48-60, depending on the number of navigators and counselors at each site). Topics will include PWID-related stigma; attitudes toward and experience with SNaP, SA, and TA

implementation packages; competing site priorities; perceptions of rewards and leadership support around SNaP; perceptions of effectiveness of SNaP, SA and TA; availability of technical assistance; beliefs around sustainability of SNaP at their test site; collaboration between HIV test sites and HIV outpatient clinics.

Quantitative characterization of high and low performing clinics: We will use the implementation test site context scales for readiness to change, implementation leadership, and implementation climate to characterize each clinic before and after implementation of SNaP. We will also characterize the test sites in terms of overall size (number of HIV tests performed), PWID size (number of HIV tests performed who are PWID),PWID proportion (number of PWID over total tests performed), staff information and current support from NGOs Clinic and PWID characteristics will be assessed before and after implementation.

Sustainment survey: We will administer the 3-question Provider REport of Sustainment Scale (PRESS) scale to site staff (including counselors and navigators) who were involved with the delivery of SNaP 6-10 months following the completion of the SNaP activities at each site. The purpose of the scale will be to assess the sustainment of the SNaP intervention at each of the sites, as well as characteristics of high and low sustaining sites. Study staff will contact site staff at the 42 HIV test sites that were involved in the SNaP study to invite them to participate in the survey. About 252 clinic staff (6 per site) will participate in the survey. Clinic staff who are interested in participating will be emailed electronic consents via a Qualtrics database to read and sign (if they choose to participate in the survey). They will then complete the fully self-administered survey on Qualtrics. The survey should take no more than 5 minutes to complete.

Sustainment in-depth interviews: We will conduct in-depth interviews with clinic navigators/counselors (n=12) and site staff or site directors (n=24) from a sub-sample of 12 of the SNaP scale-up sites at 6-month post-endline. Based on their scores on the PRESS, we will randomly select 6 “high sustainer” and 6 “low sustainer” clinics for these interviews. The purpose of these interviews is to understand how SNaP and SNaP implementation strategy adaptations influence normalization and sustainment of the SNaP intervention into HIV testing clinics after the removal of external study support. SNaP study staff will contact clinic navigators, site staff, and site directors and will invite them to participate in the interviews. All interviews will be conducted over Zoom in Vietnamese by bilingual Vietnamese research assistants trained in qualitative interviewing. Participants will provide informed consent before being interviewed. The interviews are expected to last approximately one hour. All interviews will be audio-recorded, transcribed verbatim, and translated to English.

5.5. Participant Study Procedures

Pre-implementation assessment of site context will be conducted among site directors and site staff. After implementation of the SNaP intervention at test sites (Time 0), post-implementation assessments will occur to evaluate implementation and effectiveness study outcomes.

PWID Data

PWID enrollment: All PWID who are confirmed HIV-infected will be given a brief consent form during post-test counseling. This consent will address permission to: 1) extract ART uptake from medical records at local ART clinics and 2) extract MAT uptake from medical records at MAT clinics. Note that consent for SNaP will not be explicitly requested, as it will be considered a routine clinical activity at that site upon trial initiation.

ART and MAT uptake data: To initiate ART, all persons in Vietnam must present a confirmation of diagnosis to the ART clinic. Using participants' study masked ID (MID), we will then review the medical record at ART clinics to confirm ART initiation. A similar process will be used for MAT uptake data. **These data will be extracted semi-annually.**

Viral suppression and interview data: During months 0-6 and 12-18 after implementation in each test site, a random sample of PWID will be identified for participation in the subsample cohort. These PWID will have an additional consent to allow re-contact and to obtain locator information, including a family member. A few days after diagnosis, the PWID subsample cohort will undergo a brief demographic, behavioral, mental health, and costing questionnaire, administered through the phone by a test site staff member trained and compensated to collect these data.

To enhance retention, the subsample cohort of 1500 PWID will be re-contacted every 3-4 months to maintain contact. If contact with the PWID cannot be established, the family member will be contacted in an attempt to update the locator information. Trained study staff (including training in confidentiality) will attempt to contact family members by phone. If after several attempts the family members are not reached by phone, our trained study staff will attempt to visit the home. (See also **Section 9.6.1**.)

At 12 months post-implementation at a test site, the PWID group enrolled at 0-6 months will be contacted to return to the test site, where a dried blood spot specimen will be collected for viral load testing. A brief questionnaire will also be administered through the phone. The questionnaire will address PWID's perceptions of SNaP and factors that may affect uptake of ART and MAT, including sociodemographic characteristics, injecting behaviors,, and costs (costing questionnaire will be administered to only a smaller subset of the 1500 PWID subsample cohort). The PWID will be given an incentive for participation in the subsample cohort.

At 18 months post-implementation, this process will be repeated with PWID group enrolled at 0-12 months. The costing questionnaire will only be administered at this follow-up to only a smaller subset of the 1500 subsample cohort enrolled at 7-12 months.

At 24 months post-implementation, this process will be repeated with PWID group enrolled at 0-18 month. The costing questionnaire will only be administered at this follow-up to a only a smaller subset of the 1500 subsample cohort enrolled at 13-18 months. With this approach, all PWID in the subsample cohort will be assessed for viral suppression 6-12 months after diagnosis (n=1200) (see Section 3.5.1 for explanation of n=1200); the 0-6 month group will have the 12 18, and 24 month assessments and the 13-18 month group will have the 24 month assessment (**Figure 1**).

Routine HIV Testing Data: Each test site routinely maintains a log of persons tested for HIV, including associated risk behaviors, such as injection drug use and sexual behavior. These data will be de-identified and used to provide the denominator for the total number of PWID diagnosed with HIV infection.

HIV Test Site and HIV outpatient Clinic Staff and Director Data

In each test site, directors, physicians, nurses, and other site staff will undergo brief quantitative interviews (up to 1 hour in length) at pre-implementation and at 12 and 24 months post-implementation. These interviews will be administered with Qualtrics to assess acceptability of the intervention and site context including organizational readiness to change, implementation leadership, and implementation climate (Table 1). Site staff will also undergo a 3-question survey at 6-10 months post endline, as described in Section 5.4. Qualitative in-depth interviews will be conducted after 24 months post-implementation and 6-10 months post-endline, as described in Section 5.4, at HIV test sites and HIV outpatient clinics.

5.5.1 Visit Procedures for PWID Participants: Post-implementation (Appendices I-III)

If the PWID accepts the SNaP intervention and is eligible and willing to participate in the implementation trial, the following procedures will occur as part of study enrollment:

5.5.1.1 PWID Not in Subsample Cohort (n= approx. 5000)

PWID who present to one of the 42 selected HIV test sites at any time point post-implementation of SNaP at that site will be offered the SNaP intervention, regardless of PWID participation in the implementation trial (see also **Appendix I**):

Enrollment Procedures:

Administrative, Behavioral, and Regulatory Procedures

- Informed consent to participate in the implementation trial
  - Consent will be obtained during post-test counseling at the site
- Bar code sticker placed on PWID's HIV confirmation test result card

Laboratory Evaluations

- No laboratory evaluations

12-Month and 24-Month Follow-up Procedures:

Administrative, Behavioral, and Regulatory Procedures

- None
  - No direct contact with participant for follow-up procedures
  - Only the participant's ID will be used at ART and/or MMT clinic if the participant presents to either of those clinics after enrollment

Laboratory Evaluations

- None

Post-24-Month Assessment Qualitative Interview Procedures *[among randomly selected PWID at 12 selected sites] (see* ***Section 5.4.1****):*

Administrative, Behavioral, and Regulatory Procedures

- Informed consent to participate in qualitative in-depth interview
- Qualitative in-depth interview

5.5.1.2 PWID Subsample Cohort (n=1500)

The subset of 1500 enrolled PWID will be selected to participate in a PWID subsample cohort that will provide locator and contact information, and be re-contacted to participate in study follow-up procedures (see also **Appendix II**). We will recruit all eligible PWID into this subsample cohort, until we reach the 1500 sample size. A subset of the PWID subsample cohort will be selected to complete additional costing questions at baseline and a single follow-up visit of 12 or 18 or 24 months, depending on PWID enrollment time.

Enrollment Procedures:

Administrative, Behavioral, and Regulatory Procedures

- Informed consent to participate in the implementation trial
  - Consent will be obtained during post-test counseling at the site
- Additional informed consent
  - To allow for re-contact and follow-up study procedures
- Provide locator information
- Quantitative questionnaire (through phone interview)

Laboratory Evaluations

- No laboratory evaluations at enrollment

12-Month Follow-up Procedures:

Administrative, Behavioral, and Regulatory Procedures

- Quantitative questionnaire (through phone interview)

Laboratory Evaluations

- Dried blood spot specimen collection

18-Month Follow-up Procedures:

Administrative, Behavioral, and Regulatory Procedures

- Quantitative questionnaire (through phone interview)

Laboratory Evaluations

- Dried blood spot specimen collection

24-Month Follow-up Procedures:

Administrative, Behavioral, and Regulatory Procedures

- Quantitative questionnaire (through phone interview)

Laboratory Evaluations

- Dried blood spot specimen collection

Post-24-Month Assessment Qualitative Interview Procedures *[among randomly selected PWID at 12 selected sites] (see* ***Section 5.4.1****):*

Administrative, Behavioral, and Regulatory Procedures

- Informed consent to participate in qualitative in-depth interview
- Qualitative in-depth interview

5.5.2 Visit Procedures for Test Site Directors and Site Staff Participants

See also **Appendix III**.

Pre-Implementation Baseline Assessment Procedures:

Administrative, Behavioral, and Regulatory Procedures

- Informed consent to participate in the implementation trial
- Quantitative questionnaire via Qualtrics
  - To assess HIV test site characteristics (site demographics and site context)

12-Month Post-Implementation Assessment Procedures:

Administrative, Behavioral, and Regulatory Procedures

- Quantitative questionnaire via Qualtrics
  - To assess HIV test site characteristics (site demographics and site context)
  - To assess acceptability of the intervention

24-Month Post-Implementation Assessment Procedures:

Administrative, Behavioral, and Regulatory Procedures

- Quantitative questionnaire via Qualtrics
  - To assess HIV test site characteristics (site demographics and site context)
  - To assess acceptability of the intervention

Post-24-Month Assessment Qualitative Interview Procedures *[among site staff (n=12), site directors (n=12) and HIV providers (n=12) at 12 selected sites] (see* ***Section 5.4.1****):*

Administrative, Behavioral, and Regulatory Procedures

- Informed consent to participate in qualitative in-depth interview
- Qualitative in-depth interview

6-10 Months Post-endline Assessment Procedures *(see* ***Section 5.4.1****):*

Administrative, Behavioral, and Regulatory Procedures

- Informed consent to participate in PRESS survey
- PRESS survey

Administrative, Behavioral, and Regulatory Procedures *[among site navigators/counselors (n=12), site directors/staff (n=24) at 12 selected sites] (see **Section 5.4.1**):*

- Informed consent to participate in qualitative in-depth interview
- Qualitative in-depth interview

5.6. Study Procedures for System Navigators and Counselors at Sites

Navigators and counselors are part of the Site Staff and, if they consent, they will participate in the visit procedures for Site Directors and Staff in Section 5.5.2.

Separately, as part of their work as site staff navigators/counselors at the HIV test site, at each navigator and counselor session, navigators and counselors will complete the following:

- **Maintain a log of PWID engaged in their care**.
  - This log will capture, in a simple format, the PWID's name, medical record number, and the type of encounter.
- After each navigation or counseling session, **complete a brief encounter form**, based on those used in HPTN 074:
  - The ***navigation form*** will capture the mode of communication (in-person, telephone, SMS text), ART/MAT status, availability of a social support person, duration of the encounter, and encounter content (HIV care, ART, MAT, sexual health, etc.).
  - The ***counseling form*** will capture the type of session (initial or booster), availability of social support, session focus, barriers addressed, duration, and need for systems navigation.
  - These forms will be forwarded monthly to the Hanoi study site for data entry.
- **All counseling sessions will also be audio-recorded** and reviewed periodically by site supervisors to provide feedback to counselors, as a standard procedure. Consent for audio-recording will be obtained from the study participant.

5.6.1 Quality of navigation sessions

The quality of navigation sessions will be measured by rating the navigator encounter forms. For each site, the central implementation teams will review the first 10 navigation encounter forms and a randomly selected 50% of all remaining navigation encounter forms, and rate each encounter on a 5-point quality scale from poor to excellent.

5.6.2 Quality of counseling sessions

For each site, the central implementation teams will also review the first 5 counseling session audio-recordings and a randomly selected 50% of all remaining counseling session audio-recordings and rate each on a 10-point quality scale.
For central review of recordings, identifying information of the PWID will not be provided to the central team. The quality rating forms and recordings will be forwarded monthly to the Hanoi team.

Navigators/counselors will be compensated for time *as Site Staff study participants at study visits* (Section 5.5.2), such as for their time answering study questionnaires

and in-depth interviews. However, as an implementation study, navigators/counselors will not be compensated *by the study* for their *work* as navigators/counselors at each HIV test site, as their work delivering the SNaP intervention will be run by the HIV test site.

6. SAFETY MONITORING AND ADVERSE EVENT (AE) REPORTING

6.1. Safety Monitoring

The study will be monitored through close collaboration of the study principal investigators, implementing sites, Vietnam collaborators, and the appropriate institutional review boards. Particular care is given due to the high-risk nature of this study population.

At each contact with PWID and HIV test site directors and staff, the study team will ask about any social harms experienced as a result of study. We will also provide all participants with study contact information and ask that they contact us immediately if they experience any social harm or other adverse event, such as disruption of families, acts of discrimination or physical harm. Study staff will refer people to appropriate care should an adverse event come to our attention that needs professional or medical intervention. If a social harm is reported, a short questionnaire will be administered to characterize the social harm and describe its impact. All reported social harms will be documented and communicated to the HMU IRB and the UNC IRB within 7 days.

We will establish a safety monitoring committee (SMC) comprising at least three people. The SMC will meet at the outset of the study in person then semi-annually by telephone or in person. The semi-annual SMC meeting will assess whether study objectives are being met and will ensure that benefit exceeds harm. The SMC will review the protocol, assessments, and consent forms prior to study initiation. The SMC will receive all reports of AEs at the same time that the AEs are forwarded to the HMU and UNC IRBs. Severe AEs will trigger an immediate meeting of the SMC. Additional meetings of the SMC can be scheduled, as needed, to discuss and resolve AE issues. Members of the SMC will include representatives of the government sponsored HIV test sites, an infectious disease physician, epidemiologist or other expert, and a methodologist. The SMC will submit minutes following every meeting to UNC IRB and the HMU IRB.

6.2. Adverse Event Reporting

Non-serious adverse events will be collected and recorded in the source documentation with referrals as necessary, but not reported in the database as part of this research protocol for all study participants. Non-serious adverse events will be collated and reported to the SMC for each SMC meeting. This report will be shared with the appropriate institutional review boards.

Serious AEs (SAEs) are defined per International Conference on Harmonisation (ICH) guidance and will be collected and reported on case report forms (CRFs) for all study participants. Only SAEs leading to death, life threatening SAEs and suspected unexpected serious adverse events (SUSAEs) will be reported to the PIs within 24 hours of the study site learning of the SAE, and reported to the SMC within 72 hours and the appropriate institutional review boards within 7 days from the time site staff learned of the SAE. Other SAEs will follow the reporting of non-serious adverse events.

6.3. 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 risk or "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 PIs to be expected or not. If a social impact is not unexpected, site staff will complete a detailed description of the impact using the UNC IRB's New Safety Information. This report will be reported to the SMC within 72 hours and the appropriate institutional review boards within 7 days from the time site staff learned of the unexpected social impact.

Given the status of illegal drug use, the associated social stigma and perceptions of drug users held by many members of the communities in which the study will be conducted, social harms could occur purely as a result of participation in a study targeting drug users. These could include discriminatory treatment and violence associated with possible disclosure of participants' drug or sex-related behaviors or of their HIV serostatus.

7. STUDY ASSESSMENTS AND OUTCOMES

7.1. Site-level Assessments

To assess the site characteristics, we will ask test sites (site directors and staff) to provide information at the start of the study (i.e., at baseline, pre-implementation), and at 12- and 24-months post-implementation on the following site characteristics:

Site demographic characteristics (in the past 1 month):

a. Number of HIV tests performed
b. PWID size (number of HIV tests performed who are PWID)
c. PWID proportion (number of PWID over total tests performed)
d. Sex distribution (men and women who are PWID)

Site context characteristic measures (**Table 1**):

a. Organizational readiness to change – ORIC scale
b. Implementation leadership – Implementation Leadership Scale
c. Implementation climate – Implementation Climate Scale

7.2. Implementation Outcomes (Aim 1)

7.2.1 Primary Implementation Outcome

The primary implementation outcome will be fidelity to SNaP intervention procedures (**Table 2**). Fidelity is measured as follows:

Fidelity = (% navigation sessions completed * % quality score +
% counseling sessions completed * % quality score)

Fidelity will be measured at the test site level by assessing each site's success in completing the three protocol-specified sessions (two navigation, one counseling) within the required eight- or four-week period, respectively, weighted by the central implementation team's quality rating of those sessions. Session completion will be assessed by reviewing the navigator and counselor logs, while session quality will be

assessed by central implementation team review and scoring of the first 10 and 5 of all forms (navigation) and audio-recordings (psychosocial counseling) respectively and a random 50% of all remaining forms and audio-recordings at each site, as described in Section 5.6 above. *Reviewers will be masked to the arm* when reviewing navigation forms or audio-recordings. For context, in HPTN 074, the Vietnam site achieved >85% completion of the 4 sessions in the protocol-specified windows, showing that in the context of a carefully monitored trial, high completion of appointments within an eight-(SN) or four-week (PC) window by this population is feasible.

The test site fidelity score will range from 0-200. The score will be the percentage of expected navigation sessions that are completed, multiplied (weighted) by the average quality rating of navigation sessions; plus the percentage of expected counseling sessions that are completed, multiplied by the average quality rating of counseling sessions. Thus, a site completing all navigation sessions with a perfect quality rating (100 points) and all counseling sessions with a perfect rating (100 points) would receive the maximum fidelity score of 200 points, whereas a site completing 90% of navigation sessions with an 80% average quality score (100*0.9*0.8 = 72 points) and 80% of counseling sessions with an 80% average quality score (100*0.8*0.8 = 64 points) would receive a total score of 72 + 64 = 136 points.

7.2.2 Secondary Implementation Outcomes

Secondary implementation outcomes will be penetration, acceptability, and implementation costs (**Table 2**):

- Penetration, defined as the proportion of newly diagnosed or previously diagnosed and not currently on ART PWID at test sites who are contacted by a counselor and/or systems navigator and who participate in SNaP sessions
- Acceptability, measured with the OADRI 12-item scale, is the perception that SNaP is agreeable or satisfactory by both PWID clients and test site staff.
- Costs, measured directly as non-research costs, see Sections 7.4 and 8.2.2.

7.3. Effectiveness Outcomes

7.3.1 Primary Effectiveness Outcome

The primary effectiveness outcome is ART uptake among eligible PWID (**Table 2**). ART uptake will be defined as the proportion of PWID receiving SNaP with evidence of an ART-related visit in an ART clinic. Acceptable evidence will include a clinic documentation of ART use or an ART prescription.

7.3.2 Secondary Effectiveness Outcomes

The secondary effectiveness outcomes include the following two measures (**Table 2**):

- Viral suppression, defined as an undetectable viral load on a dried-blood spot sample.
- MAT uptake, evidence of MAT use from MAT clinic records, defined as MAT initiation among those not currently on MAT

Table 2. Study Outcomes		
Outcome	**Definition**	**Measure or Scale***
Primary Integration Implementation Outcome		
Fidelity to SNaP protocol	Delivering SNaP as intended.	(systems navigation % * average quality score) + (counseling session % * average quality score) [see text for example]
Secondary SNaP Implementation Outcomes		
Penetration	% of PWID contacted, & enrolled in SNaP	Proportion of newly diagnosed or previously diagnosed and not currently on ART PWID at test sites who are contacted by a navigator and/or counselor and participate in a SNaP session.
Acceptability	Perception that SNaP is agreeable, palatable, or satisfactory.	OADRI (adapted): 12-item scale, staff and client acceptability of an innovation in a clinic setting.[25] and qualitative interviews
Implementation costs	Costs of SNaP & its implementation	Directly measured non-research costs (Aim 2)
Primary Effectiveness Outcome		
Uptake of ART	% PWID who initiated ART	ART clinic records of consenting PWID
Secondary Effectiveness Outcomes		
Viral suppression	% PWID virally suppressed	Undetectable viral load on DBS**, in PWID subsample cohort
Uptake of MAT	% of PWID on MAT	MAT clinic records of consenting PWID

*All measures will be adapted to SNaP; **DBS=dried blood spot

7.4. Cost-Effectiveness Measurements (Aim 2)

We will conduct an empirical costing study of SNaP—including SA and TA and the actual process of implementation itself—from a societal perspective. We will estimate implementation costs prospectively by embedding a trained costing specialist within each Intervention Mapping team, documenting all resources used (e.g., staff training level and time, travel costs, supplies, etc.) and estimating the unit cost of each resource. To estimate the unit health system cost of each intervention, we will perform detailed budgetary analysis including interviews of key staff, review of logbooks/timesheets, and time-and-motion studies to record navigator, counselor, and other staff time devoted to various activities on ≥15 randomly selected days, conducted by the costing specialists, in each of 12 clinic sites (6 sites per arm, selected purposively to provide representation of patient volume, urban/rural status, and geography) over the course of the trial. To estimate patient costs, we will administer a survey to a smaller subset of the 1500 PWID subsample cohort at baseline, and a single follow-up visit of 12 or 18 or 24 months, depending on PWID enrollment time to collect data on direct and indirect (lost wages, child care, etc.) costs of clinic visits and other elements (e.g., medication side effects) associated with ART, MAT, and SNaP itself. Cost data collection will be based on the Tool to Estimate Patient Costs, which we have adapted and used in Uganda.[21]

We will use, in our primary analysis, an “ingredients” or bottom-up approach, with comparison to “top-down” costing. Our comprehensive costing will include costs associated with each component of each delivery strategy (*e.g.,* staff, equipment, consumables, overheads, etc.), and will follow international conventions for all procedures including economic costing, discounting, and reporting.[26,27]

7.5. High and Low Performing Sites (Aim 3)

Our *a priori* definition of successful implementation at 24 months is a site with a fidelity score of

136 (see Section 7.2) and 70% ART uptake among its newly diagnosed or previously diagnosed and not currently on ART PWID clients.

8. STATISTICAL CONSIDERATIONS

8.1. Power and Sample Size Considerations

8.1.1 Implementation Outcomes Sample Size Calculations

The **primary implementation outcome is fidelity**, based on an index with a score ranging from 0-200 (see Section 7.2). **The unit of analysis is test site** (n=42 test sites total, 21 per arm).

In HPTN 074, the Vietnam site achieved 86%-88% completion of navigation and counseling sessions in the protocol-specified window, and in our counseling studies we consistently achieve 90-95% quality scores on supervisor-rated counseling sessions. **This track record suggests a "best case" upper bound to the fidelity score of ~150** [(100*0.85 navigation sessions completed * 0.9 quality) + (100*0.85 counseling sessions completed * 0.9 quality) = 76.5+76.5 = 153].

We expect TA to achieve *close to* this "best case" upper bound, with ≥80% appointment completion and ≥85% quality scores, or ***a fidelity score of ≥136***= (100*0.8*0.85 + 100*0.8*0.85). We expect IM to achieve lower session completion and lower quality.

Using two-tailed tests and α=0.05 and assuming a conservatively large standard deviation of 40, ***42 sites will give us 80% power to detect a difference between a fidelity score of 136 in the TA arm and 100.5 in the SA arm.***

A score of 100.5 in the TA arm corresponds to 75% session completion and 67% average quality ratings (100*0.75*0.67 + 100*0.75*0.67 =100.5).

With a more plausible standard deviation of 28, we would have 80% power to detect the difference between a score of 136 in the TA arm and 111 (75% completion,74% quality) in the SA arm. Thus, we have power to detect operationally meaningful differences in session completion and quality scores.

8.1.2 Effectiveness Outcomes Sample Size Calculations

The **primary effectiveness outcome is ART uptake**, measured as a dichotomous variable at the PWID level. After accounting for up to 12% mortality during follow-up, we estimate an available sample of 6200 PWID, with cluster (test site) size ranging from 7-764 PWID (mean≈148). **Loss to follow-up does not affect this outcome**, as patients not retained in clinic will be assumed not to be on ART.

To calculate the design effect, we estimate that the intra-cluster correlation coefficient may range from 0.01-0.05, as is typical in clinic-level behavioral interventions, implying a design effect between 2.5 and 8.4.[28-31]

*Using two-tailed tests and α=0.05, **we will have >80% power** to detect a difference as small as 10 percentage points (e.g., 70% vs. 60% ART uptake) if the ICC is as large as 0.05, and as small as 6 percentage points (e.g., 70% vs. 64% ART uptake) if the ICC is as small as 0.01.* Thus, we are well powered to detect operationally meaningful differences in our primary effectiveness outcome of ART uptake.

For viral load, which is based on a sample of n=1200 (~30 per clinic), *assuming the same ICC of 0.01-0.05, **we will have 80% power** to detect differences of 10-14 percentage points in viral suppression between arms (e.g. 40% vs. 30% if ICC=0.01; 40% vs. 26% if ICC=0.05).*

8.2. Statistical Analyses and Data Management

8.2.1 Implementation and Effectiveness Outcomes Analyses (Aim 1)

We will conduct intent-to-treat comparisons between arms, using a generalized linear regression model with an identity link and Gaussian error distribution to compare means (e.g., fidelity scores) or an identify link and binomial error distribution to compare proportions (e.g., ART uptake). For patient-level outcomes (e.g. ART uptake), the design effect introduced by clinic-level randomization will be addressed using a robust variance estimate.

Data for all aims will be managed at the UNC-Vietnam. Each site will undergo explicit training in data quality. All data sources, including electronic surveys, paper forms, and audio-recordings will be monitored for quality and completeness. Data queries will be made promptly to the sites, typically within one week. The central data team head will have group quarterly calls with site data representatives to address any ongoing data issues. Specific sites will have calls as needed.

8.2.2 Cost-Effectiveness Analyses (Aim 2)

We will estimate and compare the unit cost (per patient) of the SNaP intervention under SA or TA. Second, if there is a difference in effectiveness between arms (and the more effective option is also the more expensive one), we will conduct a comparative cost-utility analysis to identify the economically preferred option, assuming a willingness to pay of Vietnam's per-capita gross national income (GNI) per disability-adjusted life year (DALY) averted.

Cost analysis: The primary outcome will be a unit cost per patient covered and per ART uptake under SA or TA, reported both as an average cost (relative to no SNaP intervention) and an incremental cost (of tailored implementation relative to standard implementation), using the empirical cost measurements, as described above. We will also describe the major cost components and key drivers of cost (*e.g.*, patient volume or cost of ART), and conduct sensitivity and scenario analyses around these major cost items to describe the likely variation in per-patient costs across different settings. For patient-level factors, we will use multivariable regression techniques (likely after log-transformation of cost measurements, depending on the distribution of the data) to develop cost functions that describe the relationships between patient-level variables (*e.g.*, gender, distance from clinic) and patient costs under each implementation strategy.

Cost-utility analyses: We will construct a Markov model to convert the incremental cost per ART uptake (primary cost-effectiveness outcome) into an estimated incremental cost per disability-adjusted life year (**DALY**) averted. We will calibrate this model to the demographics of the trial population and incorporate a Markov structure, simulating 10,000 adults living with HIV over time steps of 6 months. Markov states will include engagement in care, ART status, viral suppression status, and engagement with MAT, and will project effectiveness outcomes observed in the trial over the lifetime of a cohort of simulated patients. We will incorporate into the model the annual probability of first-order transmission (*i.e.*, transmissions of HIV occurring from individuals in each arm). We will adopt the societal perspective, with secondary analyses from the health system and patient perspectives. We will conduct one-way sensitivity analyses across all model parameters, multi-way sensitivity analyses for those parameters found to be most influential, and a probabilistic uncertainty analysis in which all parameters are varied simultaneously using Latin Hypercube Sampling. Additional sensitivity analyses will include different assumptions about the duration of effectiveness of SNaP and scenario analyses of different economic and epidemiological conditions (*e.g.,* different country contexts). All analyses will be performed in R (R Foundation for Statistical Computing).

8.2.3 High and Low Performing and Sustaining Site Characterization- Analyses (Aim 3)

Aim 3 - Qualitative data analyses: All qualitative interviews will be audiotaped, transcribed, translated, coded and computerized for analysis using Atlas.ti v.8 software. Analysis will begin as data are collected so that topics for further exploration can be incorporated into ongoing fieldwork. Qualitative data analysis consists of the search for patterns in data and conceptualizing ideas that help explain the presence of those patterns.[32] Textual data analysis will involve five steps: 1) reading for content; 2) deductive and inductive coding; 3) data display to identify emerging themes; 4) data reduction; and 5) interpretation. Memos will be written for each code. Codes will be refined during the process of analysis. Responses of navigators and counselors, test site staff, and test site directors will be compared within and across the staff groups and within and across high and low performing and sustaining sites. For example, we will compare navigator and counselors' attitudes around implementing SNaP, including PWID-related stigma, competing job responsibilities at the site, perceived effectiveness of SNaP, and perceived status/value of being navigators and counselors, by high and low performing sites to understand if and how these attitudes may ultimately affect site performance.

Aim 3 - Quantitative data analyses: The site characteristics will be assessed with exploratory analyses to examine associations with high and low performing and sustaining clinics. Site is the unit of analysis. Given the small sample size, we will assess each site measure separately. We will use a generalized linear model with a logit link and binomial error distribution to assess the dichotomous outcome of high or low performance and sustainment. Individual implementation or demographic measures will be included as an explanatory variable, with an indicator variable for study arm, and an interaction term (assessed with α=0.10). The interaction term will aid in interpreting whether a specific characteristic modified the effect of the implementation strategy. Two sets of models will be constructed: baseline measures only and change from baseline to evaluation.

Data triangulation: IDI and quantitative data will be triangulated to understand SNaP

and SA and TA approaches within high and low performing and sustaining sites. For example, if in low performing sites, site directors scored low on the implementation leadership scale leading to low SNaP fidelity and penetration, the qualitative data could inform ***why*** site directors in these sites did not support and value SNaP (e.g. lack of prioritization of PWID clients due to PWID-related stigma), and ***how*** we can improve leadership investment (e.g. a stigma-reduction program combined with VAAC recognition of sites that improve SNaP implementation over a year). These integrated data will provide information about both clinics that "lag behind" and clinics that need less intervention for success. Although descriptive, these data will provide critical information for other settings seeking to implement and sustain SNaP.

8.3. Potential Biases and Solutions

Potential biases of this study, among both PWID and Site Directors/Site Staff participants, include selection bias during recruitment and social desirability bias during the assessments.

Social Desirability Bias

Some questions asked to the PWID subsample cohort may be sensitive. For example, we may ask about participants' drug use, injection drug use, alcohol use, sexual behaviors, HIV testing history, HIV care seeking behaviors and ART adherence. Participants may provide answers they perceive the interviewers want to hear. Social desirability bias may also occur among the Site Directors and Site Staff, as they may feel pressure to show their clinic and/or staff in a positive light.

Efforts to prevent social desirability bias and encourage accurate responses among participants include emphasizing confidentiality of all participant responses, and assuring participants that their responses and participation in the study will have no effect on the quality of their health care or access to health care (for PWID) and no effect on employment status or treatment in the workplace (for Site Directors and Staff). Also, interviewers and study staff will be trained to maintain strict confidentiality, to build rapport with participants and to ask questions in a respectful and non-judgmental way. Additionally, for Site Directors and Staff, we will ensure that their responses will not be shown to any other staff or supervisors at the clinics.

Selection Bias

Participation in the study is completely voluntary, and it is possible that those who agree and consent to participate in the study may have different characteristics from those who do not participate. In turn, difference in characteristics may be associated with differences in study results. We will minimize selection bias by assuring confidentiality to all potential participants and addressing any concerns that may arise among potential participants who are hesitant to join the study. We will also track the numbers who decline to participate in the study, providing an estimate of the extent of potential selection bias that may exist.

9. HUMAN SUBJECTS CONSIDERATIONS

9.1. Ethical Review

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

Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually. The Investigators will make safety and progress reports to the IRBs/ECs 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. The Principal Investigators and UNC Project Vietnam are responsible for the submission of continuing review to the required ethical review bodies.

9.2. Informed Consent

Electronic voluntary informed consent will be obtained from each study participant. Participants who consent to participation in the study will provide electronic signatures via tablets or laptops. The study site is responsible for developing study informed consent forms for local use that describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template form into the local Vietnamese language, and verifying the accuracy of the translation by performing an independent back-translation.

Literate participants will document their provision of informed consent by signing their electronic informed consent forms. Non-literate participants will be asked to document their informed consent by marking their informed consent forms (e.g., with an X, thumbprint, or other mark) in the presence of a literate third party witness. Participant literacy will be determined according to local site SOPs. Any other local IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

Participants will be provided with a copy of their informed consent forms if they are willing to receive them.

PWID participants: All PWID participants who are confirmed HIV-infected (n=6200) will be given a brief consent form during post- test counseling. This consent will address permission to: 1) extract ART uptake from medical records at local ART clinics and 2) extract MAT uptake from medical records at MAT clinics. Note that consent for SNaP will not be explicitly requested, as SNaP will be incorporated as a routine clinical activity. However, audio-recording of post-test counseling for purposes of fidelity measuring is not part of routine clinical activity, therefore we will obtain consent for all audio-recording the post-test counseling.

The PWID subsample cohort (n=1500) will have *an additional consent* to allow re-contact at a later date and to obtain locator information, including information of a family member.

Site directors and site staff participants: HIV test site directors and staff will provide electronic informed consent prior to quantitative and qualitative interviews.

9.3. Risks

This study does not introduce new drugs, new therapies, or new indications for existing drugs, but rather aims to understand ways to best implement the SNaP intervention to increase ART and MAT uptake, and suppress viral load.

Our study will not increase the risk of participants who present to HIV test sites. In Vietnam, it is illegal to share medical records outside the health system and this is clearly understood by all practitioners including those that provide HIV and MAT (specifically, methadone in Vietnam) related care. Based on our qualitative research with providers and law enforcement officers for HPTN 074, as well as more than a decade of experience conducting HIV studies in Vietnam, disclosure of ARV and MAT patients to law enforcement officials does not occur. Furthermore, methadone maintenance treatment (MMT) guidelines and DECREE 96/2012/NĐ-CP state that MMT patients are exempt from mandatory detoxification centers, even if MMT participation is suboptimal.

There may be some discomfort to directors and staff working in HIV test sites identified as low-performing/low-sustaining. However, we will work closely with the Vietnam Administration for HIV/AIDS Control (VAAC) to minimize this risk and minimize any risk that authorities will treat sites or staff differently based on performance identified by our study. In a pilot ART/MMT integration study among 18 clinics and 3 provinces conducted by VAAC in 2012, there were instances in which clinic staff and local leaders resisted ART/MMT integration and were not able to successfully integrate service. No punitive measures were taken against these clinics or their leaders or staff. Furthermore, during formative research our team has conducted on ART/MMT integration, clinic staff, local leaders, and VAAC representatives openly discussed barriers to integration and identified productive approaches that could be employed to overcome the difficulties that both leaders and staff may encounter.

Similarly, we do not anticipate any punitive measures to HIV test sites that are less successful in SNaP implementation or sustainment. We have worked closely with the VAAC and the National AIDS Committee for over 15 years on several sensitive projects. The VAAC is engaged and committed to providing technical support for the scale-up of SNaP in Vietnam and strongly supports this proposed research.

There will be no additional risks or side effects for participants presenting to SA sites compared to participants who presenting to TA sites.

Dried blood spots will be collected from PWID who consented to participating in the subsample cohort. Dried blood spot collection consists of a finger prick to the participant. There are minimal risks to dried blood spots, such as a slight pain when the finger is pricked. To reduce the possibility of pain, dried blood spot collection will be taken by trained staff. Participants may decline the dried blood spot collection with no consequence to their care. Participants may return for their results, and trained staff will provide results referrals to appropriate health care services as requested or necessary.

A small risk of psychological distress is posed by study questions such as those concerning HIV risk, drug use, and disclosure of HIV serostatus. Participants may find answering questions

about these issues upsetting: these questions will be asked in as sensitive a manner as possible, and participants may decline to answer at any time. If a participant experiences emotional upset during the interview, the research staff will be trained on how to handle these situations and the principal investigators will be available to speak with participants if needed.

Specific and appropriate protocols will be in place to ensure a participant's safety should a research staff member feel that a participant is in danger of harming himself or others during the course of a study visit. We will also remind participants that they can terminate the interview at any time.

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities."

Study-related visits will not be conducted in prisons or jails with study participants. Incarcerated participants will be eligible to resume study participation upon release.

Steps taken to ensure that potential participants do not feel coerced to enter or remain in the study: Research staff recruiting participants will follow a standardized script to ensure that all ethical issues are adhered to and that study protocols are followed. For PWID participants, all written and oral communications about the study will emphasize that this study is completely voluntary and will not impact employment status, or the entitlement for the MAT or HIV services, hospital or other clinics or testing sites, and that they can drop out of the research at any time without jeopardizing their entitlement to any of these services. For HIV test site directors and staff participants, all written and oral communications about the study will emphasize that this study is completely voluntary and will not impact employment status, and that they can drop out of the research at any time without jeopardizing their jobs. In addition, interviewers reviewing consent with participants will be trained to probe for comprehension.

9.4. Benefits

All PWID presenting at the 42 HIV test sites will be offered the SNaP intervention. While PWID may likely benefit from the SNaP intervention, they may not directly benefit from enrolling as participants in the study. Participants may benefit from being able to share their experiences and opinions about the SNaP intervention. Participants in the Tailored Approach (TA) implementation arm may benefit from potentially more effective implementation of SNaP. Participants in the PWID subsample cohort may benefit from knowing their HIV viral load, to discuss with their HIV care provider.

HIV site directors and staff participants may benefit from the additional service skills they observe, which may allow them to better serve their patients at the site. Site directors and staff participants may also benefit from being able to share their experiences and opinions about the different aspects of facilitating PWID into HIV care and learning about different implementation strategies and the importance of HIV test site context.

Participation in the study may put one at risk of confidentiality breach if study staff are not well trained in rigorous confidentiality safeguards, or if data are not properly encrypted and securely

stored. However, because we have highly trained and experienced team in Vietnam, with over 10 years of experience conducting complex and rigorous research studies among highly stigmatized populations in Vietnam, the risk of these data breaches is very small. Therefore the risks are reasonable in relation to the benefit of being in a study that will compare implementation strategies for a systems navigation and psychosocial counseling (SNaP) intervention.

9.5. Incentives

Pending IRB approval, PWID subsample cohort participants and site directors and site staff participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Reimbursement amounts will be specified in the study informed consent forms. PWID participants who are not in the subsample cohort will be compensated a small amount for their one-time visit.

9.6. Confidentiality

Procedures to safeguard confidentiality: All participants will receive a patient identification number (PID) and this number will be used for all interviews and collection of lab specimens. This PID will not be linked to the participant's name, and no other information that would disclose the participant's identity will be found on any interview or specimen label. Data will be kept without serostatus or injecting drug use identification in locked cabinets at the UNC-Vietnam office in Hanoi or designated offices at sites. Only the consent form, tracker form and tracker computer will link the participant's name to the identification number. If appropriate, we will maintain contact with participants using a computerized tracking system. In addition, interviewing and office staff will sign a "confidentiality pledge" prior to having contact with participants.

All study interviews and procedures will be administered by trained study staff in a private room or over zoom (in the case of the 6 month post-endline in-depth interviews). If names and identifying information are collected, a logbook will be used to link a participant's identifying information with his/her PID; personal identifiers will not be stored in the data set. The logbook will be kept in a locked cabinet, separate from all other study file cabinets, in a locked project office room; an electronic copy will be saved on a password-protected, encrypted computer. All data, notes, and audio- recordings will also be kept on a password-protected, encrypted computer. Access to the locked files and security passwords will be given only to the PIs, UNC-Vietnam In-Country Director, Research Manager and select well-trained project staff.

The logbook will be destroyed and the electronic copy deleted 9 months after the end of data collection. Tapes of qualitative interviews will be destroyed within one year of being transcribed electronically. Raw data files will be destroyed one year after electronic coding. Blood samples will be incinerated after no more than 10 years of storage in lab facilities.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIH/NIDA and/or its contractors; the US FDA, OHRP; other U.S., local Vietnamese, and international regulatory entities; and/or site IRBs.

9.6.1 Re-contacting Subsample Cohort PWID

A subsample of participants (n=1500) will be re-contacted to return to the test sites post-implementation for viral load assessments. We will ask the subsample cohort to provide contact information of family members who may be able to help us locate the participant during the study. We will only contact family members for the purpose of locating the participant; we will not ask the family members any questions other than where and when we can contact the participant. We will implement the following measures to protect the participant's confidentiality and mitigate risks of disclosure of the participant's HIV or drug use status:

1. Study identification:

   When speaking with family members of participants, study staff will not identify the study as a study of PWID or HIV-infected persons. Instead, they will refer to the study broadly as a study to better understand health in the community. Study staff will be trained in strategies to maintain the identification of the study as a general study on health in the community. They also will not disclose the study population as being PWID or HIV-infected persons.

   Any referral card from the study to ART, MMT or other health services will not disclose the participant's name, as it will contain a study ID to link the participant to the participant's study records. The referral cards also will not disclose that the referred patient is coming from a research study, but rather from the participant's local District Health Center.

2. Staff training:

   Staff's maintenance of confidentiality: Staff will sign confidentiality statements at recruitment and on annual basis regarding sharing any participant information, ensuring the privacy of participants. The confidentiality statement will give examples of the kinds of information that should be kept confidential, such as the HIV and drug use status of all participants. Additionally, all staff will maintain updated certifications in good clinical practice, human subjects protections and good participatory practice. Any staff members who do not adhere to protocols to maintain participant confidentiality will be immediately placed on 2 weeks of administrative leave and will be re-trained by one of the supervisors on the importance of and how to maintain participants' confidentiality. The staff member will be closely monitored. If the same staff is found in violation of participant confidentiality again, depending on the severity of the violation, that staff will be terminated from working for our study.

   Identifying social harms: We will train the staff in the collection and reporting of social harms, such as unintended disclosure of HIV or drug use status, and such events will be collected and reported by study staff to study leadership in a structured process.

3. Study participation:

   All participants are identified on study materials by their participant ID number only, thereby preventing their name from being disclosed and linking them to a specific study. All participants will be provided with contact information of the In-country Director and Study Coordinator, which participants may use to privately inform study leadership of any issues or concerns they have regarding their study participation.

Procedures to maintain the integrity of the data: All files will be backed up daily on project computer hard drives and on external hard drives. Files will be protected by the use of a password and encryption security system and with firewall protection from the Internet. Weekly software updates will provide additional protection.

10. LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

As described in Section 5.5.1.2, the following specimen will be collected at all study sites:

- Dried blood spot for viral load testing, collected for PWID Subsample Cohort only

10.1. Specimen Collection, Storage, Processing

Dried blood spots (DBS) can be easily prepared at district labs, using blood drawn for routine clinical examination, without special processing requirements. The filter paper used is easily obtained and stored in Vietnam. DBS can be transported and stored at ambient temperature for up to 14 days after collection. After this time, DBS must be frozen at -20^{0}C or -70^{0}C at the provincial or district labs for up to 2 years. From the district/provincial labs, DBS can be shipped in dry ice to a genotyping lab.

Site and study staff involved with specimen collection and/or management will adhere to standards of good clinical laboratory practice and SOPs for specimen collection, management, storage, and transport.

10.2. 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 United States regulations (42 CFR 72).

11. DISSEMINATION PLAN

This study will comply with all NIH and U.S. Federal governments requirements related to the dissemination of the research findings upon completion of the study. Specifically, the research findings will be disseminated through several mechanisms:

a) Presentation of the research findings at an appropriate international conference, such as CROI or the International AIDS Society conference.
b) Publication of the research findings in a suitable scientific journal.
c) Deposit of all journal publications in PubMed C in compliance with existing Federal rules and regulations.
d) Registration of the study with ClinicalTrials.gov prior to study initiation, regular updating of the protocol on ClinicalTrials.gov, and submission of the research findings to ClinicalTrials.gov upon completion of the study. All activities with ClinicalTrials.gov will be completed within the timeframes specified in the official policy.

e) Presentation of the research findings to the Vietnamese Ministry of Health and any other interested parties (e.g. governmental representatives of other Southeast Asian countries, WHO representatives from the Southeast Asia Regional Office)

In addition, to comply with current regulations, all informed consent forms will include a statement referencing that this study will be registered in ClinicalTrials.gov and will provide a link to the site to enable interested participants to review the trial information on the website.

Oversight of these procedures will be completed with assistance from the Office of Sponsored Research and the Institute of Global Health and Infectious Diseases (IGHID) Regulatory Group at the University of North Carolina. The IGHID Regulatory Group regularly tracks all clinical trials for the UNC ACTG and HPTN studies, as well as all NIH-funded studies conducted in our research sites in Malawi, Vietnam, and South Africa.

12. ADMINISTRATIVE PROCEDURES

12.1. Study Team Roles

UNC and OSU, where the PIs Drs. Go and Miller are based, respectively, will be responsible for the overall oversight and conduct of all aspects of the study (**Figure 4**). JHU will lead the cost-effectiveness and intervention implementation aspects of the study along with UNC and OSU. UNC-Vietnam and HMU will be responsible for in-country management of the study. UNC-Vietnam, HMU, and VAAC will work closely as the implementation teams for the study.

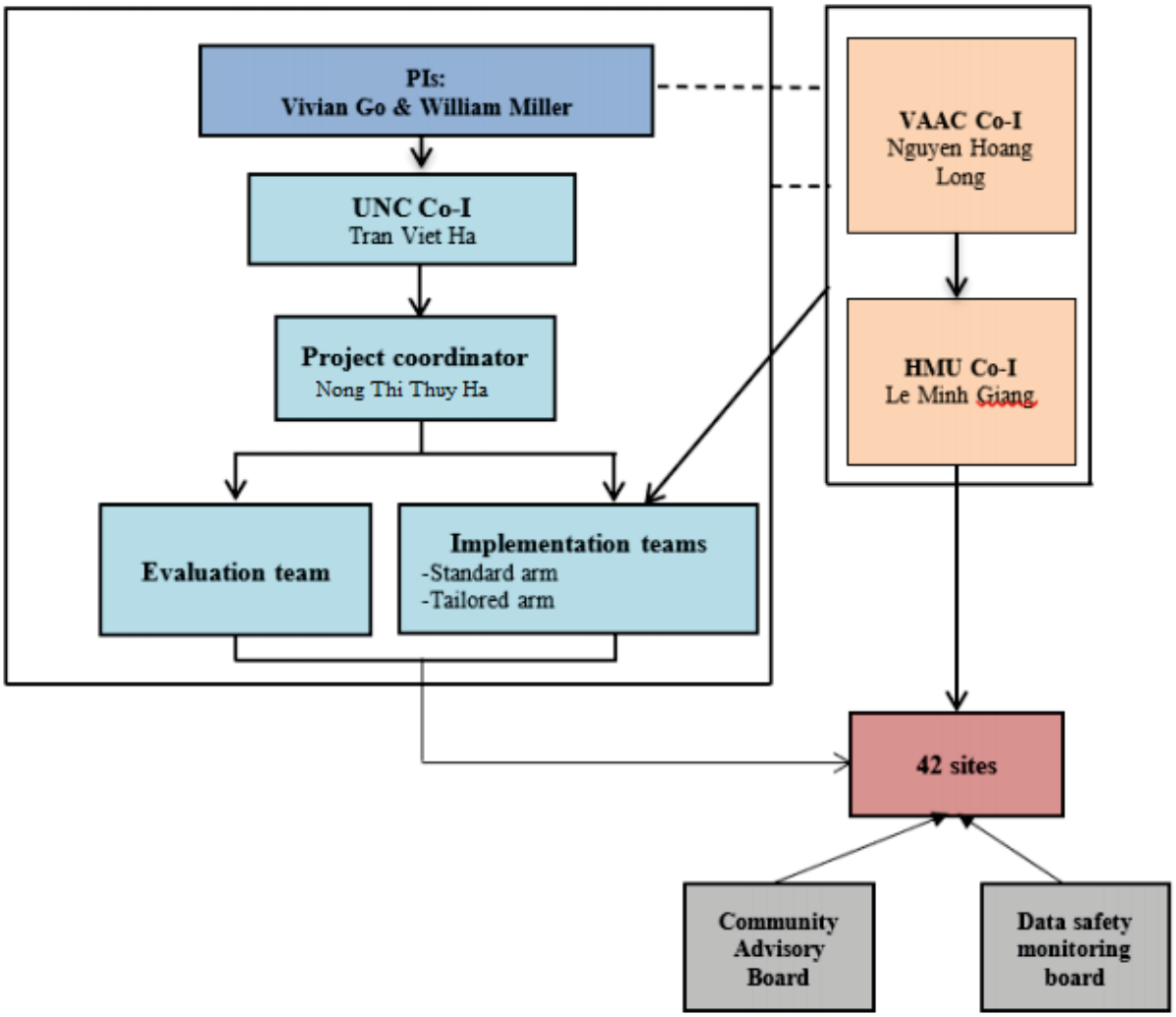


Figure 4. Overall structure of the study team**; blue is US-based, green is Vietnam-based**

Note: Implementation Teams = Central Implementation Teams (see Sections 4.2 and 5.2.1)

12.2. Study Coordination

Study implementation will be directed by this protocol as well as the SOPs. The SOPs will outline procedures for conducting study visits, data and forms processing, AE assessment, management and other study operations. The study team will develop study case report forms and other study instruments. Data will be transferred to the central UNC-Vietnam office in Hanoi, processed, and cleaned.

The data manager will be responsible for coordinating Quality Control reports and data queries resolutions.

Close coordination between the PIs and UNC-Vietnam 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, retention, and AE incidence will be monitored closely by the PIs and UNC-Vietnam as well as the SMC. The PIs will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

12.3. Study Monitoring

On-site study monitoring will be performed in accordance with SOPs. The PIs, UNC, and UNC-Vietnam teams will visit the sites 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.

A site visit log will be maintained at the study site to document all visits.

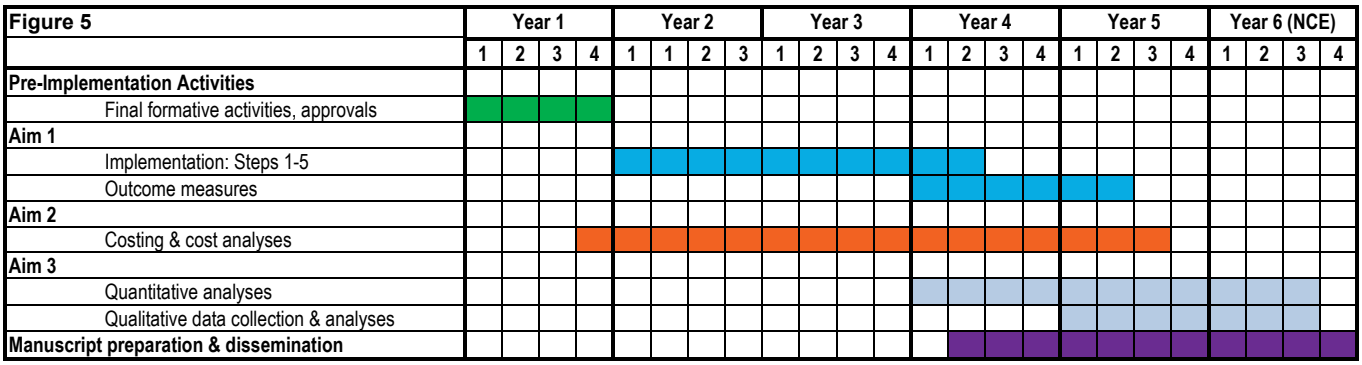
12.4. Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the PIs. All protocol amendments must be submitted to and approved by the relevant IRB(s)/Ethical Committees prior to implementing the amendment.

12.5. Use of Information and Publications

Publication of the results of this study will be governed by the PIs. Any presentation, abstract, or manuscript will be submitted by the authors to the PIs for review prior to submission.

12.6. Timeline



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APPENDIX I. Schedule of Procedures for the ***PWID participants <u>not</u> in the subsample cohort*** (n= approx. 5000)

	Pre-Implementation	**Post-Implementation**			
		Enrollment	**12mo**	**24mo**	**Post-24mo**
Administrative, regulatory, and behavioral assessment procedures					
Enrollment informed consent		X			
Additional consent					
Locator information					
Quantitative questionnaire *via interviewer*					
Qualitative interviews consent					X*
Qualitative assessment					X*
Laboratory procedures					
Dried blood spot collection					

*Only applies if participant was randomly selected to participate in post-implementation qualitative interviews.

APPENDIX II. Schedule of Procedures and Evaluation for the ***PWID Subsample Cohort*** (n=1500)

	Pre-Implementation	Post-Implementation				
		Enrollment	12mo	18mo	24mo	Post-24mo
Administrative, regulatory, and behavioral assessment procedures						
Enrollment informed consent		X				
Additional informed consent		X				
Locator information		X				
Quantitative questionnaire *via interviewer*		X	X**	X***	X	
Qualitative interviews consent						X*
Qualitative assessment						X*
Laboratory procedures						
Dried blood spot collection			X**	X***	X	

*Only applies if participant was randomly selected to participate in post-implementation qualitative interviews.

** Only applies if participant was enrolled in study within 0-6 months after implementation of the SNaP intervention at the test site.

*** Only applies if participant was enrolled in study within 0-12 months after implementation of the SNaP intervention at the test site.

APPENDIX III. Schedule of Procedures and Evaluation for ***HIV Test Site Directors and Site Staff*** *participants (including HIV providers at nearby HIV clinics)* at all 42 test sites

	Pre-Implementation	Post-Implementation				
		Enrollment	12mo	24mo	Post-24mo	6-monts post-study
Administrative, regulatory, and behavioral assessment procedures						
Informed consent	X					X
Locator information						
Quantitative questionnaire *via Qualtrics*	X		X	X		X
Qualitative consent (*)					X	X**
Qualitative assessment (*)					X	X**

(*) For HIV providers at nearby HIV clinics only
** For HIV providers at select clinics only