BRAVO

Buprenorphine to Improve HIV Care Engagement and Outcomes: A Randomized Trial

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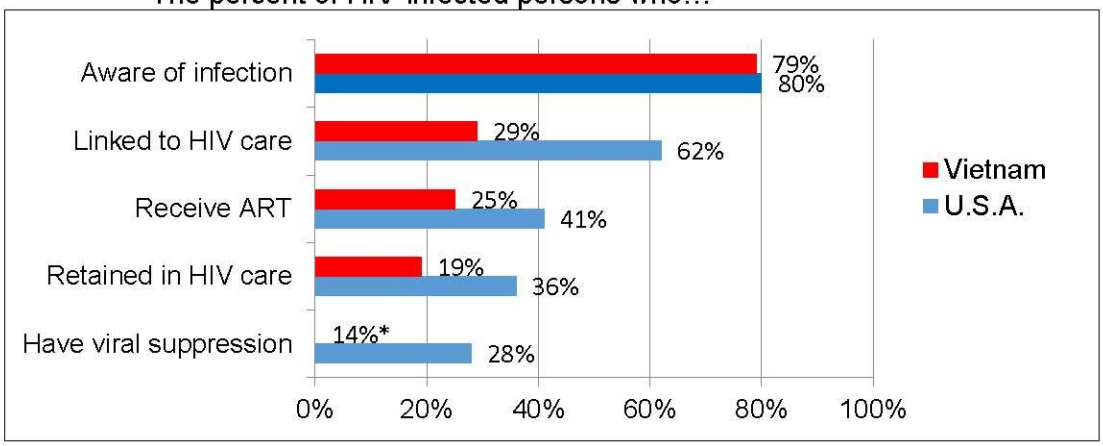
Introduction and Background

Opioid dependence worsens HIV transmission and outcomes across the continuum of HIV care.

Heroin injection drug use (IDU) is the main driver of HIV transmission in Vietnam and a recalcitrant source of new HIV infections worldwide.[5-6] In Vietnam, HIV prevalence among IDUs ranges from 20% to 56%[7]. Needle sharing among HIV-infected IDU ranges from 7% to 37%, contributing to ongoing transmission.[7] In addition to risk behavior-related transmission, opioid use amplifies transmission due to lack of HIV viral suppression in IDU who do not fully access HIV care. IDU adversely impacts engagement across the continuum of HIV care: being diagnosed with HIV in a timely manner, linking to HIV care, receiving and adhering to ART, and staying in HIV care.[3, 8-9] Successful engagement throughout this continuum is required for achieving sustained HIV viral suppression.[3] Interventions to close the gaps in engagement in HIV care are urgently needed in the U.S. and worldwide. In Vietnam, only 29% of those estimated to be living with HIV are linked to care (Figure 3).[1, 3, 10] National data regarding HIV viral suppression are limited in Vietnam (* in Figure 3). A large cohort study demonstrated 72% of ART-naïve participants achieved viral suppression at 12 months,[2] which extrapolates to 14% of all HIV-infected Vietnamese. As in the U.S., IDU are less likely to be linked to care, receive antiretroviral treatment (ART), stay in HIV care, or achieve viral suppression compared with non-users.[2, 4]

Figure 1. HIV Care Cascade in Vietnam and U.S.A.[1-4]

The percent of HIV-infected persons who…



Access to opioid dependence treatment for HIV-infected IDU is limited.

While engagement in methadone maintenance therapy (MMT) is effective for decreasing opioid use and HIV transmission, access to substance abuse treatment is limited for many HIV-infected participants in the U.S.[11-12] Barriers to MMT include requirements for observed dosing, lack of transportation[13], inflexible dosing schedules[14], legal problems[15-17], perceived discrimination and cost.[15, 17-19] Treatment of heroin dependence in Vietnam has historically involved compulsory commitment to rehabilitation detention centers for re-education where relapse rates exceeded 90% in 2011.[20] MMT scale-up has been highly successful since being introduced in 2008, with 62 treatment centers nationwide and plans for 28 new clinics in 2013. Many HIV-infected IDU in Vietnam, however, experience barriers to MMT as in the U.S. and other countries. Twenty-five percent of HIV-infected participants at participating Vietnam HIV clinics have untreated, active heroin dependence (Table 1). New treatment delivery models are urgently needed to augment MMT scale-up and improve access to treatment. A 2012 change in Vietnamese government policy encourages voluntary and community-based addiction treatment

as an alternative to compulsory rehabilitation, and opens the door for testing addiction treatment models that better engage HIV-infected IDU at all levels of the HIV care continuum (Vietnam Government Decree 96 modification, 2012).

Clinic-based BUP/NX: potential for improving engagement in the HIV care continuum. Training HIV providers to manage opioid dependence with buprenorphine/naloxone (BUP/NX) during HIV clinic visits has the potential to expand access to opioid dependence treatment while increasing engagement in HIV care. Buprenorphine/naloxone (BUP/NX), a partial opioid agonist recently available in Vietnam, has few drug-drug interactions with HIV or TB treatment medications, low overdose risk, no requirement for daily observed dosing and avoids the administrative requirements of MMT, making it highly feasible for use in busy HIV clinics.[21-23] As in other countries, HIV providers in Vietnam's 320 HIV clinics are well-positioned to adopt new treatments and successfully manage both HIV and opioid dependence as two interrelated chronic, but treatable illnesses. Studies of BUP/NX in HIV care settings are limited, however. Two U.S. pilot studies of BUP/NX suggest it is safe and feasible and reduces opioid use in HIV care, but were limited by lack of a comparison group[21-22], and small sample size.[24] In both studies, the majority of participants were already on ART with high baseline rates of viral suppression, limiting the capacity to assess the effect of BUP/NX on HIV outcomes. Assessing the effectiveness of clinic-based BUP/NX with a high proportion of participants new to care, as we propose, provides the opportunity for assessing its ability to close gaps in the HIV care cascade in real-world HIV clinic settings.

Clinic-based BUP/NX: potential for decreasing HIV transmission. Treating IDU for opioid dependence decreases risky injection and sexual HIV transmission risk behaviors as well as opioid use.[25-26] In a recent meta-analysis of 12 studies that examined the association between opioid agonist therapy (OAT) for opioid dependence and HIV incidence, OAT reduced new HIV infections by 54% (rate ratio 0.45; 95% CI 0.32, 0.67).[27] Likewise, treating HIV-infected persons for HIV decreases HIV viral load—the main host determinant of HIV transmission—and decreases transmission apart from change in risk behavior.[28] Combining ART and MMT for IDU in Vancouver, British Columbia decreased new HIV infections both among IDU and in the community, overall.[29-30] BUP/NX delivered in a primary care setting decreased HIV transmission risk behaviors in one single-center, observational study.[26] HIV viral load is the primary driver of infectivity. If our proposed trial of clinic-based BUP/NX is effective in increasing viral suppression, fewer new HIV infections will occur among the sexual and drug using partners of opioid dependent individuals.[28-30]

Clinic-based BUP/NX is an innovative addiction treatment delivery model in much of the world.

Healthcare settings are traditionally underutilized as potential sites for expanding addiction treatment, both in the U.S. and other countries. Within Vietnam and developing and middle-income countries, our work is innovative because it tests a novel services delivery model for medication-assisted treatment of opioid dependence in healthcare settings that are already seeing large numbers of participants with opioid dependence. The dominant treatment for heroin dependence in Vietnam is compulsory commitment to a 2-year government rehabilitation center for re-education, administered by the Ministry of Labor, Invalids and Social Affairs (MOLISA) with relapse rates of 70- 90% in 2011[20]. MMT programs have expanded rapidly since 2008, but access remains limited, as in much of the rest of the world.[29-30] Integrating addiction treatment into clinic-based settings is an alternative treatment model with the potential for efficiently expanding access to other medication-assisted treatments for addiction.

Objectives

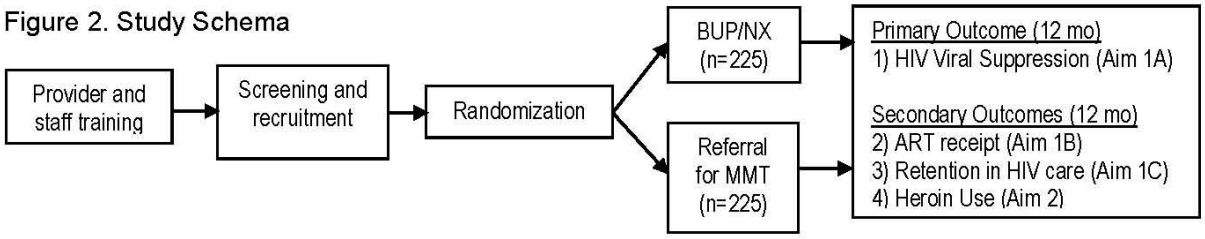
The primary objective of this proposal is to add to the palette of treatment options by comparing the effect of two opioid dependence treatment delivery models on improving the HIV care engagement and outcomes in Vietnam. We propose a multisite, open-label, randomized, flexible-dose noninferiority trial of buprenorphine/naloxone (BUP/NX) (n=225) versus methadone maintenance therapy (MMT) referral (n=225) for treatment of opioid dependence in HIV-infected participants in 6 Vietnam HIV clinic research sites. The study is conducted in partnership with colleagues at Hanoi Medical University (HMU), the Provincial AIDS Control (PAC) authorities of Hanoi, Thanh Hoa, and Bac Giang, the Vietnam National Institute of Mental Health, and Oregon Health & Science University.

Study sites are 4 HIV clinics in Hanoi, 1 in Thanh Hoa, and 1 in Bac Giang; epicenters of Vietnam's HIV and heroin epidemics, all of which are associated with MMT and HIV testing and counseling centers. A research coordinating center at HMU provides additional outreach, recruitment, non-medication-related study procedures and links participants to participating HIV clinic sites for clinical management. HIV providers will be trained to manage opioid dependence using BUP/NX.

Participants are HIV-infected participants with opioid dependence new to HIV care, recruited from HIV clinics, MMTs, and associated HIV testing centers. Participants randomized to BUP/NX will receive BUP/NX after successful completion of medication induction and stabilization. Participants randomized to BUP/NX will receive a taper after 12 months of study drug exposure, with referral for MMT. Participants randomized to MMT will receive usual care, which is case-manager-assisted referral to MMT. All participants receive clinic-based individual counseling and HIV care.

The primary outcome of HIV-1 viral load will be measured at baseline, 6, and 12 months. Secondary outcomes, including self-reported drug use, urine drug screens (UDS), and measures of HIV care engagement (adherence, retention) will be assessed quarterly through 12 months follow-up. Qualitative interviews with participants, family members of participants, and providers in years 1 through 4 will identify lessons-learned for scale-up of HIV clinic-based BUP/NX.

Figure 2. Study Schema



There are three specific aims in this protocol:

Aim 1: Assess effect of clinic-based BUP/NX versus MMT referral on HIV treatment engagement and outcomes in HIV-infected participants with opioid dependence. The associated hypotheses are:

- H1a: Participants randomized to BUP/NX will have noninferior rates of HIV viral suppression (HIV-1 RNA < 200 copies/mL) on 12 month blood draw compared with MMT referral.

- H1b: Participants randomized to BUP/NX will have greater (Antiretroviral Therapy) ART initiation, adherence, and retention in HIV care at 12 months versus MMT referral.

Aim 2: Assess effect of clinic-based BUP/NX versus MMT referral on opioid use in HIV-infected participants with opioid dependence. The associated hypothesis is:

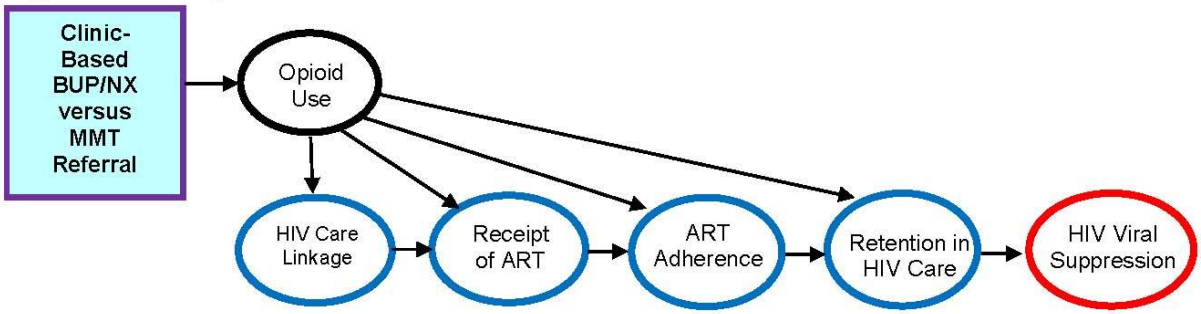
- H2: Participants randomized to BUP/NX will have a lower proportion of positive assessments for opioid use (self-report + UDS) at 12 months versus MMT referral

Aim 3: Assess BUP/NX implementation experience to inform national scale-up of clinic-based BUP/NX.

Conceptual Model

Substance use disorders impair participant engagement and retention in HIV care, contributing to gaps in the HIV care cascade.[3, 34] The current study seeks to compare clinic-based BUP/NX versus referral for MMT for treating opioid dependence in HIV-infected participants to improve engagement and retention in HIV treatment that leads to HIV viral suppression (Figure 2). Virologic suppression reduces HIV associated morbidity, prolongs survival, restores and preserves immunologic function and decreases HIV transmission [35]. As shown in the conceptual model below, decreased use of opioids (Aim 2) and uptake of and adherence to ART (Aim 1B) are proximal outcomes that contribute to virologic suppression (Aim 1A). HIV-infected Injection Drug Users (IDU) who initiate ART should be able to achieve virologic suppression within 6-12 months if they continue in HIV care and adhere to ART.[36-38] In this model, successful treatment of opioid dependence is hypothesized as an important moderator of HIV care engagement and subsequent viral suppression. HIV-infected IDU who receive treatment for substance use are more likely to use HIV care and receive ART.[39-41] Participant and provider attitudes toward treatment and organizational characteristics, assessed in Aim 3, influence adoption of new treatment modalities and provide lessons learned for wide-scale implementation.[42] The Consolidated Framework for Implementation Research (CFIR)[43-44] suggests that participant, provider, and organizational factors are key inputs to adoption of new evidence-based technologies in healthcare (Aim 3).

Figure 3. Conceptual Model



Setting

Hanoi, Thanh Hoa, and Bac Giang are epicenters of the Vietnam HIV epidemic with high numbers of HIV-infected heroin users. Care innovations in these provinces often serve as models for others to follow. Six outpatient HIV clinics (OPC) will participate in the clinical trial as clinical research sites: 4 clinics in Hanoi (Tu Liem, Long Bien, Hoang Mai and Dong Da), 1 clinic in Thanh Hoa (Thanh Hoa PAC OPC), and 1 clinic in Bac Giang (Bac Giang PAC OPC). A

research coordinating center at HMU provides additional outreach, recruitment, non-medication-related study procedures and links participants to participating HIV clinic sites for clinical management. HIV clinics were selected based on the prevalence of untreated active opioid dependence among new participants with a history of IDU, ability to enroll at least 120 participants over the course of the study, availability of methadone maintenance, and support of local authorities. Medical directors at participating sites estimate that < 5% of participants with active heroin use currently access MMT. All HIV clinic sites have on-site counseling, case management, phlebotomists and pharmacy services on-site, and are affiliated with Voluntary Counseling and HIV Testing (VCT) services and MMT programs in their surrounding communities that have capacity for accepting new MMT referrals.

Study Design and Procedures

450 Participants (225 BUP/NX and 225 MMT) HIV-infected participants with active opioid dependence will be enrolled in the study across participating sites. Outreach activities will seek to identify patients new to HIV care or registered for care at participating HIV clinics but not on ART, though participants are not required to be ART treatment-naïve. Participants will be enrolled in the study for approximately 12 months, with 6 research visits total.

Inclusion Criteria:

- HIV positive
- Have a current moderate to severe DSM-5 opioid use disorder
- Urine drug screen positive for opioids
- Interested in receiving treatment for opioid dependence
- Are age 18 or greater
- Are willing to practice effective method of birth control, if female

Exclusion Criteria:

- Have a known hypersensitivity to buprenorphine or naloxone
- Have an AST & ALT > 5x upper limit
- Are currently pregnant or breastfeeding
- Have a serious medical or psychiatric illness in past 30 days (e.g. opportunistic infection, psychosis) that precludes safe participation in the opinion of study physician
- Have received methadone maintenance treatment within 30 days of consent

Known vulnerable populations will be excluded from participation; this includes children, pregnant women, decisionally-impaired adults, and prisoners.

Prisoners:
Groups and organizations that work with newly-released prisoners will also be included but will not approach individuals who are currently detained as prisoners. There is no probation or parole program in Vietnam. Researchers will meet with staff and volunteers, provide study information, and provide referral information only. No direct contact between newly-released individuals and research staff will occur.

Research staff at each clinic and at HMU have been instructed on procedures related to participants who become incarcerated during enrollment. During incarceration, no research procedures will be conducted. If a participant is released during the twelve-month study period, research procedures may be resumed.

Participants will be given wallet cards with instructions to the police that they contact the research site for more information. In Vietnam, a suspected drug user will not be detained if he is voluntarily receiving treatment. Participants will be instructed on how to use the wallet card.

Recruitment Methods
Recruitment will occur through HIV clinics that will collaborate with their associated Voluntary Counseling and Testing Centers (VCTs) and MMTs to identify newly diagnosed participants. Local community groups (e.g. charity, non-profit, international organizations, self-help, peer educators, etc) and other governmental agencies, groups, and clinics will be contacted and provided with study information so that they can refer HIV+ and/or opioid dependent individuals to the clinic. Research staff will distribute flyers describing the study and provide contact information. Research staff will also participate in traditional outreach methods and offer HIV rapid testing (finger-prick) within the IDU community and will perform pre-screen activities outside of the clinic. These pre-screening activities will include HIV rapid testing and urine drug screening as location allows. Location of "outside of the clinic" could refer to anyplace; including parks, peer meetings, non-research clinics, etc. Anybody pre-screening as eligible will be given detailed instructions for referral. This type of recruitment will not only increase enrollment numbers but will increase the public health awareness of HIV and substance use screening.

Groups and organizations that work with newly-released prisoners will also be included but will not approach individuals who are currently detained as prisoners. Detailed instructions will be provided to Vietnamese colleagues about the distinction. Researchers will meet with staff and volunteers, provide study information, and referral information only.

HIV clinic staff will screen participants at intake for study eligibility. HMU research coordinating center research staff and peer educators will approach people from community-based "hot-spots" and from people participating in existing observational research studies to offer study participation. Potential participants with a history of MMT within the past 30 days will be excluded and encouraged to follow-up with their MMT program, in order to avoid creating an incentive for participants already engaged in MMT to switch to BUP/NX. HIV clinic and research staff will approach potential participants and assess inclusion and exclusion criteria.

Consent process
Participation in the study is completely voluntary.

HIV clinic research staff will review study procedures with potential participants and collect informed consent. Study procedures will comply with International and U.S. requirements for human participant protections. Consent forms will be approved by Institutional Review Boards at OHSU and HMU, and by the Vietnam Ministry of Health Ethics Review. All consent forms will be presented to candidates in Vietnamese and will be administered by Vietnamese-speaking research staff.

There are four consents used in this study:
1. Pilot testing of study measurements
2. Pre-Screening
3. Full Study
4. Qualitative Interviews (participants, family members, providers and administrators (staff))

Compensation
All participants will be compensated for their time and effort in this study, using culturally-appropriate amounts. All compensation will be in cash and provided at the end of each visit so no pro-rating will be necessary. The following schedule will be used.

Table 1. Compensation Schedule

Visit	Amount in Vietnamese Dong	Amount in American Dollars (approximate as of October 2016)
Pre-Screening	50,000₫	$2.24
Screening	200,000₫	$8.97
Baseline	200,000₫	$8.97
3 Month	250,000₫	$11.21
6 Month	300,000₫	$13.46
9 Month	350,000₫	$15.7
12 Month	450,000₫	$20.19
TOTAL	1,800,000₫	$80.70

Those who participate in pilot testing receive a one-time amount of 100,000₫. Those who participate in the qualitative interviews will receive 200,000₫ for each interview.

Travel reimbursement will be provided for research visits only (not medication induction or other medication dispensing visits) at the rate of 3,000₫ per kilometer.

Participants will not pay for the following research-associated laboratory testing:

- Screening: CBC, AST/ALT, CD4
- Baseline: Hepatitis B, Hepatitis C, tuberculosis screening (PPD test), HIV viral load, HIV confirmatory testing when only rapid test results available, HIV genotype resistance for participants on ART and who have viral loads > 200.
- 6 Month: CD4 and HIV viral load
- 12 Month: CD4, HIV viral load, HIV genotype resistance for participants on ART and who have viral loads > 200

Referral Compensation

- Participants can refer individuals to the study, and upon successful completion of randomization, receive 100,000₫.
- Community outreach groups (peer educators, self-help, etc) can refer individuals to the study, and upon successful completion of randomization, receive 300,000₫. Outreach workers will receive 50,000 for each person pre-screened, regardless of randomization.

Insurance Payments
Beginning January 1st, 2017, the government of Vietnam is requiring health insurance for HIV-infected patients. For those unable to obtain other insurance, the study will pay for insurance premiums while they are enrolled in the study. This will be coordinated with Hanoi Medical University and Hanoi PAC (Provincial AIDS Center) and payments will be directly made to the insurance companies, not to participants. Currently, this is expected to cost about 680,000 VND ($30 US dollars) per year but could be change per national or local policy. Without the study paying for insurance, some participants would likely become ineligible to receive antiretroviral therapy, thus biasing the study's secondary outcomes as well as jeopardizing retention rates.

Randomization
Participants are randomized to clinic-based BUP/NX vs. referral for MMT. This is a non-blinded study. Randomization will be conducted by computer generated random number sequence in blocks of 10 prepared by statisticians at OHSU. Allocation assignments will be maintained in sealed, sequentially numbered envelopes by the Vietnam Research Coordinating Center (RCC) at Hanoi Medical University. HIV clinic site research assistants will call the RCC to receive allocation assignment when a participant is deemed eligible for study participation.

Pilot Data Collection and Assessments
The data collection instruments were pilot-tested with participants at four additional sites: Bac Giang PAC OPC; Bac Giang Provincial Hospital OPC; Viet Tri, Phu Tho PAC OPC; and Phu Tho Town Community Health Center OPC.

Table 2: Table of Assessments								
	Pre-Screening	**Screening**	**Baseline**	**3 Month**	**6 Month**	**9 Month**	**12 Month**	**As Needed Only**
Visit Window	--	60 days after Pre-Screening		+/- 14 days	+/- 14 days	+/- 14 days	-14 days/+30 days	--
Pre-Screening Consent Form	X							
Informed Consent		X						
Informed Consent Quiz		X						
Progress Note		X	X	X	X	X	X	X
Visit Checklist	X	X	X	X	X	X	X	
Locator Form	X	X	X	X	X	X	X	
Master Enrollment Log	X	X	X					
Communication Log								X
Compensation • **Log** • **Receipt**		X	X	X	X	X	X	
Data Collection Forms								
Inclusion/Exclusion Criteria (Eligibility Checklist)			X					
Pre-Screening Survey	X							
Screening Survey		X						
Baseline Survey			X					
3 Month Survey				X				
6 Month Survey					X			
9 Month Survey						X		
12 Month Survey							X	
ASI-lite Table			X	X	X	X	X	
Randomization Form			X					
Physical Exam			X					
Dosing Form • **BUP/NX** • **MMT**				X	X	X	X	
HIV Care Utilization Form				X	X	X	X	
Fatal Overdose Form								X

Table 2: Table of Assessments								
	Pre-Screening	**Screening**	**Baseline**	**3 Month**	**6 Month**	**9 Month**	**12 Month**	**As Needed Only**
Pregnancy and Birth Control Assessment • **Includes Urine Test**		X	X	X	X	X	X	
Confirmed Pregnancy Test								X
Early End of BUP/NX								X
HIV Viral Load			X		X		X	
CD4*		X*			X*		X*	
HIV genotype resistance testing (as necessary)			X				X	
HIV confirmatory testing (as necessary)		X						
HIV rapid testing	X							
Tuberculosis (PPD Skin Test)*			X*					
Hepatitis B/C*			X*					
Safety Labs* • **CBC** • **AST/ALT** •		X*						
UDS • **Morphine** • **Methadone** • **Methamphetamine** • **Amphetamine** • **Buprenorphine**	X	X		X	X	X	X	
Adverse Events • **Paper Log** • **eCRF** • **Serious Adverse Events eCRF**								X
Protocol Deviation • **Paper Log** • **eCRF**								X

Table 2: Table of Assessments								
	Pre-Screening	**Screening**	**Baseline**	**3 Month**	**6 Month**	**9 Month**	**12 Month**	**As Needed Only**
Study Termination Form							X	X (if ppt ends early)
**chart abstraction possible*								

Visit Procedures

Survey Data

Research assistants will administer participant surveys in a confidential setting using real-time, secure, web-based electronic data entry. All survey measures have been translated into Vietnamese and been field tested and adapted for cultural appropriateness and feasibility for electronic data collection in Vietnam during previous research.

Survey data measurements include:

- Demographics
- Drug and alcohol use
- Addiction treatment
- HIV treatment
- Co-morbid conditions including physical and mental health
- Quality of life

Medical Chart Data

Research assistants will review participant HIV clinic and MMT medical charts quarterly to inform outcome measures including receipt of ART, retention in care, and adherence to study treatment condition (buprenorphine, methadone dosing, counseling visits). Medical charts will be reviewed at Baseline to establish diagnoses of Hepatitis B, Hepatitis C, and Tuberculosis. If not available in medical chart, research staff will obtain testing as necessary.

Biologic Data

Urine samples for pregnancy and urine drug screens (morphine, methamphetamine, methadone, amphetamine, buprenorphine) will be collected and processed in the HIV clinic using point of care testing.

Viral load specimens will be drawn at baseline, 6, and 12 months, and processed for transport at HIV clinic, then transported to the National Hospital for Tropical Disease for centralized lab testing. HIV viral load testing (the primary outcome) is performed with Real-time RT-PCR on Real-time ABI 7500 machine with reagents and primers made by Invitrogen.[110] The current viral load technique is certified for a lower limit of HIV-1 RNA detection of 55 copies/mL.

All other phlebotomy measurements (Safety Labs, and CD4) will be either drawn at the appropriate times following the above schedule or will be chart-abstracted as required. They will be drawn and processed for analysis at the HIV clinic locally.

Study physicians will conduct baseline physical exams to assess for medical appropriateness for participation.

Qualitative Data

Annual in-depth interviews with a purposefully-driven sample of participants, family members, providers, and administrators will be conducted by research assistants in years 1-4. During annual site visits (years 1-4), we will conduct audio-recorded qualitative interviews with:

1. Providers (n=5 per site) including HIV clinic physicians, nurses, counselors, and pharmacists responsible for the care of participants at the clinic and for referral and treatment for substance use disorders
2. Administrators (n=2 per site) who lead the clinics and local HIV prevention authorities,
3. Participants (n=10 per site, five per randomization arm) to document their experience with care.

4. Family Members (n=10 per site), identified as a support person by the participant

Site visits observe practices for BUP/NX clinical procedures, counseling, and referrals for MMT. The study team will complete site visits each year (years 1-4) completing approximately 68 interviews per year across all four sites. Interview guides use the Consolidated Framework Implementation Research (CFIR) framework to probe participant perceptions of the characteristics of the BUP/NX and referral (e.g., intervention quality, advantage, adaptability), outer setting (e.g., resources, external policies and incentives), inner setting (e.g., clinic organization, networks and communication, practice culture, and implementation climate), provider characteristics (e.g., knowledge and beliefs about BUP/NX and substance abuse and self-efficacy) and the implementation process (e.g., engaging, executing, evaluating).[43-44] Not all questions will be asked of all informants based on interview responses. Interview guides are meant to guide the conversation.

Randomization Arms

Clinic-based BUP/NX

HIV clinic providers and staff will be trained in BUP/NX management of opioid dependence. Participants randomized to clinic-based BUP/NX will be evaluated by the HIV clinic study physician for symptoms and signs of withdrawal using clinically available opioid withdrawal scales and induced onto BUP/NX when in moderate withdrawal in order to avoid precipitated withdrawal (12-24 hours after last dose of short-acting opiates like heroin, and 2-4 days after last dose of long-acting opioids. BUP/NX induction begins with a 2-4 mg test dose followed by additional doses on the day of induction to relieve withdrawal symptoms, and then titrated to a maintenance dose between 8-24 mg/day over 1 to 3 days. Participants will return for daily dosing until a stable maintenance dose is reached, as determined clinically by the HIV clinic study physician. Dosing will remain flexible to a maximum dose of 24mg. After a participant is stabilized on a maintenance daily dose for at least 2 weeks, they may switch to every-other-day dosing (4 times per week), doubling the maintenance dose to a maximum of 32mg prior to “skip” days. Participants will continue to receive BUP/NX for 12 months, followed by a 14-day taper and referral to MMT. The study will use BUP/NX in a 4:1 ratio combination sublingual tablet for treatment of opioid dependence.

Referral for MMT

Referral for MMT has become the standard of care for opioid dependence in Vietnam. Participants randomized to MMT referral will meet with an HIV clinic case manager who will facilitate referral to MMT. Methadone dosing will be managed by MMT staff, who dispense methadone according to Ministry of Health guidelines for MMT.[98]

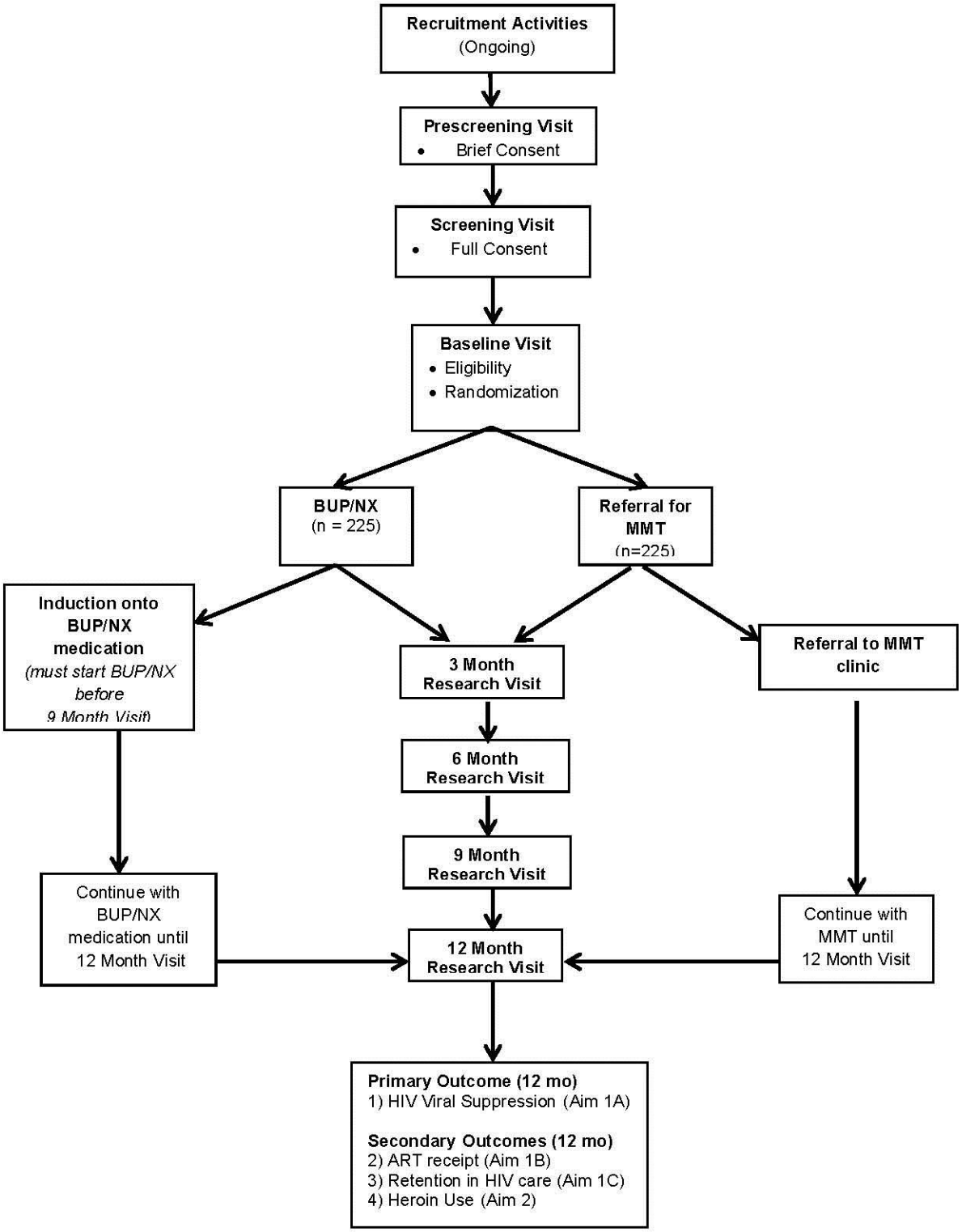
Study sites and dosing sites

Participants will complete all research activities (consenting, surveys, and other data collection activities) at the six HIV clinics. Two HIV clinics (Tu Liem clinic and Long Bien clinic) will serve only as clinical management and medication dispensing sites, with non-medication study procedures being performed by Vietnam Research Coordinating Center (HMU) research staff.

If a participant becomes unable to travel to the study clinic because of serious illness or injury, study staff or appointed clinic staff will be allowed to distribute buprenorphine as needed to ensure continued substance abuse treatment. Hospital or home dosing must continue to be approved on a case-by-case basis by the Principal Investigator to ensure clinical safety. Approval will also only be on a case-by-case basis to ensure that non-clinic dosing is only being used in the most serious of cases when there is no other option for a participant to remain on study drug. Current national buprenorphine guidelines allow for take-home dosing for those

unable to travel to clinic. Study staff will maintain current drug accountability procedures including completion of dosing logs and pill counts.

Figure 4. Detailed Study Flow



Risks and Benefits

Risks

In addition to the risks associated with the study medication (either arm), there are several general risks associated with participating in a clinical trial.

Risk of Underlying Conditions

Each of the participating HIV clinic research sites have established practices for managing medical emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each research site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action. As this population will have significant ongoing health and substance use issues, events related to complications of HIV, substance use treatment or admission for substance detoxification, hospitalizations for medical and psychological reasons and deaths will be captured on study specific forms and not duplicate reported as an adverse or serious adverse event. These data will still be included in the reports to the DSMB at the regular meetings.

Risks to Confidentiality

There are also risks to confidentiality, particularly because information will be collected about substance use and abuse and other potentially illegal activities.

Phlebotomy Risks

Blood drawing may cause pain or bruising at the site and carries a small risk of infection.

Buprenorphine/Naloxone

The study will use BUP/NX in a 4:1 ratio combination sublingual tablet for treatment of opioid dependence. Potential adverse events related to BUP/NX include: death, which has been reported among people who abuse BUP in combination with benzodiazepines and other drugs; withdrawal, if BUP is taken while actively taking methadone or various other opioids; increased risk of opioid dependence with continued use of heroin or other opioids; and possible impairment of mental or physical abilities for at least 6 hours after taking BUP.

Because it is a partial opioid agonist, BUP/NX has limited respiratory depressant effects, low toxicity even at high doses, and limited risk of overdose. At sufficient doses, BUP/NX blocks the effects of exogenous opioids and can both reduce illicit use and afford some level of protection against overdose. BUP/NX has abuse potential, though in contrast to full agonists like methadone, this is limited, likely also a consequence of partial agonist properties. Buprenorphine itself may cause physical dependence. It can also cause intoxication and mild respiratory depression, as evidenced by possible drowsiness and breathing that is slower and shallower.

Common side effects from BUP may include headache, constipation, difficulty sleeping, weakness, sleepiness, nausea, vomiting, sweating, and dizziness. Elevated liver enzyme levels have been reported in participants with hepatitis who are treated with buprenorphine.

If the participant attempts to dissolve and inject BUP, he/she may experience opioid withdrawal symptoms, including nausea, diarrhea, hot and cold sweats, hot flashes, muscle cramps, flushing, painful joints, yawning, restlessness, watery eyes, runny nose, chills, gooseflesh, sneezing, abdominal cramps, irritability, backache, tension and jitteriness, depression, sleepiness, shaking or tremor, sensitivity to noise, clammy or damp skin, or other unpleasant

effects. Use of other opioids while receiving the BUP tablet could also result in opioid withdrawal symptoms.

Though BUP/NX is metabolized by cytochrome P-450 3A4, a prime pathway for antiretroviral metabolism, clinically significant drug-drug interactions with HIV or TB-related treatments are rare. Known P450 inhibitors such as erythromycin, ketoconazole, and the HIV protease inhibitor atazanavir can increase BUP levels. Despite this, there was no difference in mean BUP/NX dose and no episodes of over-sedation among the BHIVES clinical trial participants taking atazanavir versus a non-atazanavir regimen after 12 months of follow-up. Inducers include phenobarbital, carbamazepine, and phenytoin which could reduce BUP levels and lead to withdrawal symptoms though this has not been observed clinically, likely because the BUP metabolite nor-BUP also has partial agonist effects at the mu receptor.

Methadone

Methadone differs pharmacologically from BUP/NX in that it is a long-acting full agonist at the mu opioid receptor that produces cross-tolerance to superimposed opiates (e.g., heroin). As a full agonist, however, there is no clear ceiling effect to its respiratory suppressive effects and thus can cause overdose in opiate naïve people or when the rapidity of dose increase exceeds tolerance. To mitigate the risks of methadone exposure to opiate naïve individuals, methadone is highly regulated and directly observed daily dosing is required.

Methadone has multiple clinically significant drug-drug interactions with ART and medications used for treatment of tuberculosis. Methadone decreases clearance of zidovudine which can lead to increased zidovudine toxicity (e.g., anemia). Other commonly prescribed ART increase methadone metabolism (e.g., efavirenz, nevirapine, and lopinavir/ritonavir), potentially requiring high doses of methadone to relieve withdrawal symptoms, and requiring methadone dose tapering to prevent unintentional overdose when ART is stopped. Nearly all HIV-infected participants in Vietnam are prescribed at least one ART medication that requires methadone dose adjustments. Rifampin, an anti-tuberculosis agent commonly prescribed in Vietnam, decreases methadone levels and may require increased methadone doses to avoid withdrawal symptoms.

Potential Benefits

Participants may benefit from participation in the proposed study by engaging in treatment for both HIV and opioid dependence. Both buprenorphine and methadone have a strong history of improving opioid dependence outcomes across many studies, worldwide. Individual findings may be helpful in participants' clinical care if they wish the data to be shared with their clinicians. Involvement in the study may positively affect the chances of abstinence.

Data Analysis

Aim 1: Assess the effect of clinic-based BUP/NX (n=225) versus MMT referral (n=225) on HIV treatment engagement and outcomes in HIV-infected participants with opioid dependence.

- H1a: Participants randomized to BUP/NX will have noninferior rates of HIV viral suppression (HIV-1 RNA < 200 copies/mL) on 12 month blood draw compared with MMT referral.

- H1b: Participants randomized to BUP/NX will have greater ART initiation, adherence, and retention in HIV care at 12 months versus MMT referral.

Overview. Aim 1 assesses the effect of clinic-based BUP/NX on HIV treatment engagement and outcomes using the study procedures outlined in the Study Design and Procedures section.

Dependent variables: The primary outcome for Aim 1 is HIV viral suppression at 12 months (lab data, binary). HIV viral suppression is defined as an HIV-1 RNA PCR test < 200 copies/mL, using the ultra-sensitive HIV real-time PCR assay available at the NHTD laboratory, consistent with current U.S. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.[35] The rationale for this definition is to avoid the influence of "blips" in HIV RNA viral load which commonly occur at levels between 20 and 200 copies/mL using current PCR assays and which are of limited clinical significance [132-133]. Secondary outcomes for Aim 1 include ART initiation at 12 months (binary, chart review); 100% ART adherence at 12 months (binary, self-report), and retention in HIV care at 12 months (binary, chart review).

Potential Covariates: We will consider participant demographics, alcohol and other drug use, HIV history, comorbid conditions, attitudes toward treatment services, and social support characteristics as potential covariates.

Power Analysis: This study was initially conceived and powered as a superiority trial. Based on a desire to augment the existing treatment options rather than justify a preferred pharmacotherapy, the design was revised with approval from the study sponsor (see attached approval letter from sponsor). For reference, the original power analysis is below:

> Sample size calculations are based on the Aim 1 primary outcome of HIV viral suppression (HIV-1 RNA < 200 copies/mL). We estimate that 340 participants will be required (170 BUP/NX, 170 MMT) to detect a 15% difference in HIV viral suppression between the two study conditions at 12 months, assuming 80% power, alpha of .05, and a viral suppression of 50% in the referral for MMT group. We increase the sample size to 450 participants (225 BUP/NX, 225 MMT) to conservatively account for potential loss to follow-up of 20%. This sample size calculation is additionally conservative in that it does not account for multiple-time-point data that will be available from our longitudinal study. We favor a conservative estimate to off-set the complexity of our proposed mixed logistic model in the data analysis.

Noninferiority Margin: For the primary outcome of viral suppression, we pre-specified a non-inferiority margin of ≤13% in the risk difference (RD) comparing BUP to MMT. The noninferiority margin was selected based on margins ranging from 10% to 15% for noninferiority trials testing the effect of antiretrovirals on HIV viral suppression. After choosing the 13% margin, we conducted an informal survey of national HIV-addiction treatment experts who confirmed that it was clinically relevant and appropriate

Data Analysis Plan: Univariate statistics will be used to describe participant characteristics and study outcomes using mean/SD for continuous variables and percentages for categorical variables. Independent samples T-tests will be used to test bivariate differences between the main independent variable (clinic-based BUP/NX versus MMT referral assignment) and baseline continuous variable participant characteristics (e.g., age, CD4 nadir, etc.). Chi-square/Fisher-Exact test will be performed to assess differences between the main independent variable and categorical variables.

The primary analysis for this study will be a mixed logistic regression model comparing BUP/NX versus MMT on viral suppression rates over time. Treatment comparisons will be performed under the Intent-to-Treat (ITT) criterion; participants will be analyzed in the arm to which they

were randomized regardless of subsequent events. In this mixed logistic model, each (binary) outcome serves as a dependent variable; treatment effect (BUP/NX versus MMT referral) and time effect (e.g., baseline, 6, and 12 months) will be considered main effects. An interaction between these two main effects, e.g., treatment*time, will be included in the model. Model-fitted, marginal risk and RD estimates will be obtained at each time by applying an inverse-logit transformation to coefficients from the logistic regression model, with standard errors estimated via the delta method. We will test the primary hypothesis of noninferiority by comparing the lower bound of a 95% confidence interval to the prespecified margin (i.e., 13%); if the lower confidence limit of the RD is greater than -13%, we will conclude that the BUP/NX is noninferior to MMT. The model will include subject-level random intercepts in order to account for repeated measurements within individuals. Attrition is unavoidable in a longitudinal study; in our study, we anticipate an attrition rate of 20%. The mixed model approach is a recommended strategy for handling missing data in clinical trials under the assumption that the data are missing at random.

We will conduct three sensitivity analyses. First, we will assume data are missing not at random and use single imputation of unsuppressed for missing VL data. Participants who are lost to follow-up will be imputed as treatment failures (i.e., not suppressed). Death from any cause and dropout will also be considered equivalent to non-suppression for the purposes of this analysis. Second, we will use multiple imputation with Markov-Chain Monte Carlo methods and "auxiliary variables" (i.e., covariates that are not part of the main analysis, but may help predict data missingness) to address missing data. We will include covariates associated with missingness at any time-points (using a relaxed p-value of 0.2) as auxiliary variables in our multiple imputation model. Finally, for our third sensitivity analysis, we will conduct a per-protocol analysis among participants who received at least one dose of study medication in the 90 days before each visit. If sensitivity analysis results change the primary outcome findings, we will report the results alongside our main analysis.

Secondary outcomes including binary ART initiation, ART adherence, and retention in HIV care will be analyzed using similar procedures. As these are superiority hypotheses, we will test them using two-tailed tests at an alpha level of .05.

Aim 2: Assess effect of clinic-based BUP/NX versus MMT referral on opioid use in HIV-infected participants with opioid dependence.

- H2: We hypothesize that participants randomized to BUP/NX will have a lower proportion of positive assessments for opioid use (self-report + UDS) at 12 months versus MMT referral

Overview. In Aim 2, we assess the effect of clinic-based BUP/NX on opioid use as measured by urine drug screens or any self-reported use in the last 30 days, assessed at 3, 6, 9, and 12 months following randomization.

Dependent variables. The primary dependent variable for Aim 2 will be the proportion of positive assessments for opioid use at 12 months, as measured by any self-reported opioid use or positive urine drug screen during the 12-month follow-up assessment (binary). We will consider secondary substance use outcomes including proportion of follow-up visits with a positive assessment for opioid use (proportion), and other illicit drug use (binary), and alcohol use (binary).

Power Analysis: Since our primary outcome in this aim is opioid use, the power analysis is based on this outcome. With our proposed sample size (450 as the total, 225 for each treatment arm), we have gained the power of 91% to detect 15% in difference between the two groups at

the level of alpha 0.05, provided that the proportion of UDS positive for opioid at 12 months will be 65% for MMT referral. This power analysis is conservative due to not maximizing multiple-time-point data from our longitudinal study. We anticipate the power is much higher to off-set the complexity of the mixed logistic model (adjusting for some covariates) we propose in the data analysis plan (see below).

Data Analysis Plan: The primary (binary) outcome for Aim 2 is opioid use, collected at baseline, 3, 6, 9, and 12 months. We will use an approach as in Aim 1.

Aim 3: Assess BUP/NX implementation experience to inform national scale-up of clinic-based BUP/NX.

Overview. We will conduct qualitative interviews with HIV providers, administrators, and opioid dependent participants, and their family members in participating HIV clinics annually during years 1 through 4 to document and describe formative implementation strategies, challenges, and best practices. Results inform policy-making for national scale-up of clinic-based BUP/NX in Vietnam.

Qualitative Procedures and Analysis. The implementation aim documents the experience of providers and participants at clinics to further inform adoption of BUP/NX in Vietnam and guides planning efforts and policy-making. Data also monitor the performance of the sites and qualitative interviews provide critical detail for enhanced understanding of the findings from the trial (Aim 1 and 2). Using the Taxonomy of Mixed Method Designs [134-136], our design has a QUAN +Qual structure with simultaneous data collection and emphasis/weight placed on the quantitative efforts. The qualitative data provide complementary information to illuminate and expand the findings from Aims 1 and 2.

The qualitative data (recurrent and salient themes extracted from interviews) document provider, organizational, and participant experiences over time to concurrently monitor clinic-based BUP/NX and to examine these findings in parallel with outcomes data (i.e., opioid use, HIV viral suppression). The HIV clinics' characteristics and provider attitudes (inner setting), as well as detail about the use of BUP/NX (intervention characteristics), and community awareness, linkage across service settings, and policy support (outer setting) help identify the full range of complex variables associated with implementation of clinic-based BUP/NX. This approach represents an innovative strategy to integrate available quantitative study results (Aim 1 and 2) to examine the provider, participant, organizational, and policy-level changes that influence the uptake of BUP/NX in HIV clinics in Vietnam. Results are compared for convergence and the team examines concordance and discordance between study sites and across populations including providers, participants and administrators. Corresponding with the Consolidated Framework Implementation Research (CFIR) we identify individual, organizational and contextual characteristics that influence uptake of BUP/NX within the context of an RCT in HIV clinics in Vietnam.

Qualitative Analysis. Data will be catalogued in a spreadsheet within one week of a site visit to assure that all files and documents have been collected. Field notes written on site are expanded and recorded electronically within 24 hours.[137] Audio-recorded site visit interviews are professionally transcribed, reviewed and summarized. Transcriptions are password protected and stored on a secure network and uploaded into qualitative analysis software (Atlas.ti™) which organizes data and facilitates coding and thematic analysis. The qualitative analysis will be completed in Vietnamese. Selected samples of the transcripts will be translated into English and sent to trained research staff so they can review and assist in developing codes. The qualitative

team creates a coding scheme, practices coding, and revises in an iterative group process that has been successfully implemented by the study team in other mixed-methods projects.[47, 138-141] Each transcript is coded and check-coding is completed with 20% of transcripts to ensure inter-coder reliability. Selected texts for each code will be translated into English for review by the U.S. investigator. The analysis examines the implementation process and identifies specific characteristics that facilitate use of BUP/NX in HIV clinics within the framework of the RCT (Aim 1 and 2). Iterative analyses assess convergence of CFIR participant, provider and organizational dimensions on study measures as well as the context of the policy subsystems, cross system interactions, and resource allocation. The team analyzes site visit products and identifies areas for additional data collection, assesses and ensures data quality, and produces summaries of findings shared with the Advisory Board to inform project implementation. A five phase strategy guides the analysis: describe themes, organize and structure data, connect codes and themes, corroborate and triangulate, and condense and summarize findings.[142]

Privacy, Confidentiality, and Data Security

Data will be stored in a manner intended to preserve participant confidentiality. All paper files that contain study data with PHI will be kept at the study sites in locked cabinets behind locked doors that only study staff have access to. Study files with names or other identifiers are kept in a separate locked cabinet than files with study data. The only file linking the unique identifier with the participant's name is the Master Enrollment Log which is kept in separate locked cabinet than any study data.

Data will be collected using the OHSU REDCap™ electronic data collection system. REDCap™ (Research Electronic Data Capture) is a secure, web-based database application designed to support traditional case report form data capture for research studies. Data files are securely maintained behind the OHSU firewall, and not shared with other institutions. REDCap™ also facilitates data quality assurance.

Computers at each site connected to the internet will be used to collect data that is directly entered into the REDCap™ database. At no time is information stored on the study site computers. Only the PIs and and research staff will have access to study data. Each participant will have a unique participant ID number; participant names will not be included in the database. The PI will work with the study personnel to verify data accuracy via monthly internal data audits.

Data and Safety Monitoring

Safety monitoring will be performed by the study's Scientific Advisory Board, who will oversee ongoing trial progress to assure protection of participants' safety while maintaining that the study's scientific goals are being met. The DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, evidence that study procedures should be changed, or if the trial should be halted (for safety, efficacy, or recruitment or performance reasons). This process is intended to assure the IRBs, sponsor, and investigators that participants are provided with an accurate and ongoing risk evaluation when participating in research trials.

Monitoring will begin with the initial review of the protocol during the study development process and continue throughout the study with meetings at least annually. Recommendations and reports from these reviews will be distributed to the site lead investigator for submission to their IRB.

The Study Coordinator will be responsible for reporting adverse events or unanticipated problems to the responsible PI within 24 hours, by telephone, for serious events (participant death, or breach of confidentiality). Other events or deviations are reportable to the PI by telephone or email within 5 working days of discovery. The PI will notify the IRB of reportable events according to IRB regulations. OHSU is the IRB of record and all reportable events will be submitted with the required timelines. HMU follows international standards for AEs and SEAs as set by the ICH.

The Principal Investigator will review or provide consultation for each serious event as needed. These reviews will include an assessment of the severity and causality of the event to the study intervention (drug or therapy) or other study procedures.

The study staff will be trained to monitor for and report Adverse Events and Serious Adverse Events. For the purposes of this study, all Serious Adverse Events will require reporting in the data system. Adverse Events that are determined to be Mild and Not Causally Related to Study Drug will not be reported in REDCap™ but will be tracked on a paper log at each site which the Quality Assurance monitors will review at all site visits.

Local research assistants will be responsible for data collection. The PI and Quality Assurance Monitor will work with the study personnel to verify data accuracy via monthly internal data audits.

See separate Data and Safety Monitoring Plan for more information.