Providing comprehensive harm reduction via telemedicine for PWID using syringe services programs: a feasibility study

1. Introduction

The U.S. South is suffering from alarmingly high rates of both opioid misuse and new HIV infections, including two counties in North Carolina: New Hanover and Mecklenburg. Wilmington, located in New Hanover County, has the highest rate of opioid prescription misuse in the nation, with misuse occurring among 12% of individuals who received an opioid prescription [1]. Studies have shown that when opioids are misused, there is a higher tendency towards injection use and transitioning from prescription opioids to heroin [2-6]. Mecklenburg County, home to the largest city in North Carolina - Charlotte, is ranked first in North Carolina for rates of newly diagnosed HIV infections [7], and has one of the highest rates in the U.S. As such, Mecklenburg County has been identified as a priority area for the national program *Ending the HIV Epidemic* (https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview). Although the HIV prevalence among people who inject drugs (PWID) in these two counties, or in North Carolina overall, is not known, the high rates of both HIV and injection drug use warrant targeted efforts.

To help reduce HIV transmission associated with North Carolina's opioid epidemic, legislation was passed in July 2016 legalizing free syringe services programs (SSPs). In the Wilmington area, there are currently one fixed site and three mobile sites for syringe access. In Charlotte, there are three fixed sites for syringe access. Together, these organizations, who will serve as community partners in this project, have dispensed over 1,000,000 syringes in 2018-2019, serving approximately 5,000 participants and represent tremendous progress towards HIV prevention in North Carolina.

Successful HIV prevention programs for PWID are comprehensive and should offer resources that are accessible and acceptable to the target population. Along with SSPs, these resources include medications such as daily oral pre-exposure prophylaxis (PrEP) with tenofovir/emtricitabine, and combination buprenorphine and naloxone (bup/nx) for opioid use disorder. PrEP has been proven effective for reducing HIV acquisition among PWID [1, 8]. Similarly, medication for opioid use disorder (MOUD) with bup/nx has been shown to significantly reduce cravings, overdoses and death [9]. In addition, because bup/nx reduces cravings, it can result in decreased injection drug use and needle sharing, which decreases the risk for drug-related HIV risk behaviors [10]. While both PrEP and MOUD are FDA approved – they remain underutilized, particularly among people who use drugs, for a variety of reasons including lack of awareness, cost, and lack of providers and/or access [11-14].

Providing PrEP and MOUD via SSPs represents one way to reach PWID, a particularly difficult to reach population. In 2018 we collected primary data from PWID attending SSPs, many of whom were at risk for HIV. Participants reported that they would be interested and willing to take PrEP and would prefer to access PrEP at SSPs (versus going to a medical clinic or health department). Building on this preliminary research, we will conduct a feasibility study in which we will provide both PrEP and MOUD for PWID utilizing SSPs in New Hanover and Mecklenburg counties. To facilitate access to care, telemedicine will be used for follow-up visits. Prior studies have shown no difference in outcomes between patients receiving opioid use disorder treatment through telemedicine or from face to face encounters [15, 16]. Similarly, there have been successful strategies for telemedicine-delivered PrEP [17].

Given that the national opioid epidemic continues to escalate with alarming consequences, including heightened risk of new HIV infections, we think there is a critical need to identify novel ways to provide harm reduction to this population. Partnering with SSPs and providing follow up through telemedicine will create an innovative and much-needed opportunity to provide evidence-based prevention strategies for a difficult-to-reach population.

2. Purpose and study objectives

The **purpose** of this study is to provide medication for opioid use disorder (MOUD) with buprenorphine and naloxone, or bup/nx, and pre-exposure prophylaxis (PrEP) for HIV prevention for persons who inject opioids accessing syringe services programs (SSPs), as part of a comprehensive harm reduction program, and assess the acceptability and feasibility of using telemedicine to implement the program.

The initial visit will be conducted either in person or remotely via telemedicine given COVID-19 protocols at the SSP sites in Charlotte and Wilmington; follow-up visits will be conducted via telemedicine. The study will include a site coordinator at each site and a central study coordinator. The site coordinators will be trained phlebotomists, responsible for follow-up visit scheduling and coordination, and collection of urine and blood samples. The central study coordinator will be responsible for participant screening, formal consenting, and collection of baseline and follow up participant questionnaires.

The **study objectives** are the following:

a) To assess uptake and persistence to bup/nx and PrEP as part of a comprehensive harm reduction program among people who inject drugs using SSPs.
b) To assess feasibility and acceptability of implementing a telemedicine-based MOUD and PrEP program among program implementers
c) To assess feasibility and acceptability of participating in a telemedicine-based MOUD and PrEP program among users (*this objective will be assessed in an ancillary protocol*)

3. Study population and setting

The study population is people who inject drugs, specifically opioids, and who access services at SSPs. The settings is the SSP sites in Wilmington in New Hanover County and Charlotte in Mecklenburg County.

4. Study design

We plan to enroll 20 PWID (10 at each site) accessing the participating SSP sites in Charlotte and Wilmington, NC. Participants will be enrolled in the study for 6 months. At the end of the study, they will be referred to MOUD and PrEP providers identified in the community.

5. Eligibility, sample size, recruitment, and data collection

***Eligibility*:** Participants must have a history of self-report injection opioid use in the past 6 months, participate in SSPs, be HIV negative, willing to take bup/nx and PrEP for 6 months, have no medical contraindications for these medications such as history of renal failure or bone diseases, not be pregnant and be 18 years or older. In addition, participants must not currently be taking PrEP or any form of MOUD, and have either a history of sharing injection or drug preparation equipment or risk of sexual acquisition of HIV (such as engaging in sex work or men who have sex with men) in the past 6 months.

Exclusion criteria: Positive pregnancy test, positive HIV test at enrollment, altered mental status in which participant cannot sign a consent form, or evidence of renal failure (estimated creatinine clearance <60 mL/min) will be cause for exclusion from the study. Although hepatitis B is not necessarily a contraindication to PrEP use, participants who are hepatitis B surface antigen positive will be excluded from this study and referred to an experienced hepatitis B and PrEP provider.

In the event that a participant becomes incarcerated during the course of the study, the study team will withdraw the participant from the protocol and cease any ongoing study activities, including ongoing data collection. If a participant becomes pregnant on study, they will also be withdrawn from the study, and all efforts will be made to link the pregnant woman to PrEP and MOUD services in the community without lapse. For participants who withdraw from the study, all data already collected will be stored securely within the Duke electronic medical record.

***Sample size*:** We plan to enroll 20 PWID (10 at each site). If a participant drops out before completing the 6 months, we will consider enrolling another participant to fill the spot. Participants will be allowed to stay on study even if they stop taking one of the paired medications.

Recruitment: Participants for this study will be clients of the SSPs who have expressed interest in the study. Participants will be recruited through the primary fixed SSP in Charlotte and through the fixed SSP in Wilmington. There will be recruitment flyers hanging in the SSP central offices, and additional recruitment flyers may be placed in the supply bags provided to SSP clients. These fliers will direct people to reach out to the central study coordinator or ask SSP staff/site coordinators to facilitate the connection with the study coordinator.

The central study coordinator will perform a short screener with SSP clients who are interested in participating in the study to ensure they are eligible for participation. Their answers will not be used as data, only determine whether we can schedule an appointment to go through the formal consent.

The study provider/primary investigator (PI), and the central study coordinator will be on site or remote via telemedicine due to COVID-19 protocols during enrollment visits to conduct participant consenting, and obtain baseline surveys. The site coordinator will be on site to complete laboratory testing.

Informed consent: At each site during the enrollment visit, identified participants who are interested and eligible will sign a consent or e-consent to enroll in the study. This consent will be provided by the central study coordinator, who has completed all necessary Research Ethics

training and undergone Duke's informed consent training. The study provider/PI and the study coordinator will be able to answer any questions or concerns about the consent in person or remotely given COVID-19 protocol.

The participant will then meet with the study provider/PI to conduct the initial visit.

Data collection:

Enrollment visit:

- *Consent and baseline data collection*: Participants will be given information about the study and about MOUD and PrEP in general. If interested, participants will provide written informed consent or e-consent using REDCap. After signing the consent form, participants will be provided with a baseline self-administered survey to collect demographics, HIV risk behaviors, and substance use history. Specific questions will include 1) previous drug, alcohol, and needle use, 2) sexual practices; 3) demographic questions; 4) recent or previous incarceration, 5) frequency of participation in SSPs and secondary syringe access sites, 6) HIV risk perceptions, 7) awareness of PrEP, 8) interest in taking PrEP, 9) history of HIV testing, and 10) health services utilization.

- *Initial visit with the* study provider/PI: The initial study visit will take place in person or remotely via telemedicine in response to COVID-19 with the study provider/PI after the participant has been consented and completed the baseline survey with the central study coordinator.

During the initial visit with the study provider/PI, participants will undergo laboratory testing including:

- HIV antigen/antibody (2 mL), comprehensive metabolic panel (1 mL) including serum creatinine and liver function tests, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody (hepatitis serologies total 4 mL)
- Urine pregnancy (if female, under the age of 55 years, and without documented sterilization)
- Urine toxicology screening

Labs will be drawn by the site coordinator on site, and will be picked up by a local LabCorp representative. The total amount of blood requested is 6 mL at the initial visit. The participants cannot remain in the study if they refuse the lab draws or pregnancy test (if female). However, they can refuse the urine toxicology screen.

All study activities will occur in a safe, confidential, and private space at the SSP. Results from the lab testing will be available in 1-2 days after the lab draw. Participants who receive a positive HIV test will be counseled by the study provider/PI per CDC guidelines [18] and referred to the respective county health departments (or primary care provider, if patient prefers) for confirmatory testing. HIV testing is performed at the New Hanover and Mecklenburg Health Departments free-of-charge Monday to Friday. Bus passes will be offered to participants needing HIV confirmatory testing, and study staff will follow up with those individuals. Because HIV is a reportable disease in North Carolina (NC), all participants will be advised that their contact information will be submitted to NC Department of Health and Human Services (NCDHHS) if they test HIV positive, and that a NCDHHS Disease Intervention Specialist will

then contact them to facilitate entry into care. Being HIV positive is an exclusion for this study, and participants will be informed of this.

All participants who receive a positive hepatitis C test will be referred for hepatitis care in Charlotte or Wilmington. Participants will be given the referral information and encouraged to call for follow-up. Hepatitis C does *not* exclude an individual from participation and these persons will be encouraged to participate in the study. Participants with a positive hepatitis B surface antigen will be excluded and referred to the appropriate medical provider (as mentioned above).

Medications

Bup/nx requires induction, and office-based prescription guidelines will be followed closely. A too gradual induction may precipitate withdrawal. Typically, participants on day 1 will be given a total induction dosage of 8 mg of bup/nx. On day 2, the dose can be increased to 16 mg, which is the common recommended target dose. Subxone® comes as a sublingual film and participants will be advised to keep it out of sight and reach of others, especially children. The participant will be advised that they have to start bup/nx when they are in withdrawal (typically 12 hours from last opioid dose) or else it will trigger withdrawal symptoms.

Tenofovir disoproxil fumarate/emtricitabine (trade name Truvada®) for PrEP is very well tolerated and taken once daily. Tenofovir alafenamide/emtricitabine (trade name Descovy®) for PrEP will not be used in this study as it has not been studied in persons who inject drugs. Participants will be advised of the 'start up' syndrome which includes some nausea, flatulence and gastrointestinal distress typically in the first 2 weeks. Participants will also be advised that it can take up to 20 days before maximum intracellular concentrations of the medication are reached in the blood and that they should take other precautions to prevent HIV in that time period.

Bup/nx will be provided free of charge to all participants through grant funding. PrEP (or Truvada®) will be obtained through the participant's medical insurance or if uninsured, the Gilead Advancing Access Program (https://www.gileadadvancingaccess.com). The paperwork for the Gilead assistance program will be completed by the study coordinator in conjunction with Walgreens (see below). For persons who are insured, Gilead co-pay cards will be provided to offset any costs of the medications.

Participants will be able to access their prescriptions for both Suboxone® and Truvada® at a designated local Walgreens in the Wilmington/Charlotte area, where the study team has set up a contract and the pharmacy is aware of the program and will provide support. Participants can also choose to have their Truvada® delivered by the specialty/mail-order Walgreens in order to avoid potential issues with transportation. Mail order is not an option for Suboxone, however, and participants will need to pick up the medication weekly from Walgreens in the local area. There is a possibility that these weekly visits can be extended to biweekly, decided by the study provider/PI.

Follow up visits:

Follow-up visits with the study provider/PI will be conducted via telemedicine (also referred to as *telehealth*), scheduled by the site coordinator. For the first month (Month 1), there will be weekly telemedicine visits conducted by the study provider/PI with each study participant to ensure that they are stable on the appropriate bup/nx dose. In a private location in each SSP, participants will be able to access the Duke MaestroCare telehealth platform. This platform enables secure, encrypted, and effective audio/video communication between the participant and provider. The study provider/PI and SSP site will use the Duke telehealth platform with an embedded camera, and the platform will transmit real-time audio and video captured by high-definition camera and integrated microphone. Both endpoints encompass a secure and encrypted platform approved by Duke Health System Information Security. The site coordinator will be present to provide technical assistance with the telehealth platform.

Starting at Month 2, the telemedicine visits will take place monthly. At that point, participants should be stable on the appropriate bup/nx doses. Participants will be asked to complete a questionnaire at Month 3 and Month 6 which include questions on HIV risk and drug use, as well as adherence evaluation for both bup/nx and PrEP.

Lab testing during follow up visits

During the weekly telemedicine visits for Month 1, the site coordinator will perform urine toxicology ('tox') screens weekly on site (although not mandatory) and urine pregnancy tests weekly for female participants on site unless an alternative form of contraception can be confirmed. Starting at Month 2, urine tox screens and pregnancy tests (for females) will be requested at monthly visits.

At Month 3 and Month 6, participants will have blood drawn by the site coordinator to test for HIV antibody/antigen and a repeat comprehensive metabolic panel. Labs will be picked up by LabCorp and results sent directly from LabCorp to the study provider/PI. The total amount of blood for follow up visits is 3 mL.

Unscheduled visits

Participants will be able to contact the study provider/PI on an unscheduled visit basis as needed. The site coordinator will reach out to the provider by pager/cell phone/email, and if possible, a telemedicine visit will be set up. Direct phone calls with the study provider/PI will also be an option if there an urgent medical question. In the event of an urgent medical problem, participants will be referred to their primary care provider or an urgent care/emergency room in their area.

Of note, the study provider/PI is an infectious disease physician with 15 years of experience treating persons with HIV. She has conducted many HIV clinical research trials including working with PWID in SSPs. She is the Medical Director of the Duke PrEP Clinic which has treated >300 persons for PrEP. She is an experienced buprenorphine provider who frequently participates in the UNC ECHO Lab case conferences which provides support and mentoring for MOUD. She also has worked with the Duke Telehealth Office on telemedicine-related activities and has their support for this project.

Schedule of study activities (all visits to occur at SSP)

Week	Description of visit
Week 1 *Enrollment Visit*	*Consent and demographics:* participant consent; baseline questionnaire *Initial visit with the study provider/PI:* screening; baseline laboratory investigations; patient assistance application for PrEP; prescriptions sent to pharmacy; begin medications
Week 2	Telemedicine visit; urine tox screen; urine pregnancy test
Week 3	Telemedicine visit; urine tox screen; urine pregnancy test
Week 4	Telemedicine visit; urine tox screen; urine pregnancy test 1st interview* conducted at the end of the first month
Month 2	Telemedicine visit; urine tox screen; urine pregnancy test
Month 3	Telemedicine visit; f/u questionnaire; laboratory investigations (including urine tox and pregnancy tests)
Month 4	Telemedicine visit; urine tox screen; urine pregnancy test
Month 5	Telemedicine visit; urine tox screen; urine pregnancy test
Month 6	Telemedicine visit; f/u questionnaire; laboratory investigations (including urine tox and pregnancy test); final interview*

*Information on interviews in ancillary protocol

6. Data analysis

The total number to treat will be 20 (10 at each site) as this is a pilot/feasibility study. We will consider enrolling new participants if there is an early withdrawal.

For Objective 1, we will use descriptive statistics to describe the baseline characteristics of the sample, including their demographics, sexual and injection risk behaviors, history of substance abuse, perceptions of and interest in MOUD, and awareness of and interest in using PrEP.

For Objective 2, we will collect feasibility information such as how many times the PI and study coordinator travelled to the SSP site, how many telemedicine visits occurred per participant, how long the visits lasted, how many were rescheduled or did not happen on time. Similar information will be collected from SSP staff who participated in this program.

By the end of the study, we hope to determine the following:

1. The proportion of persons who demonstrate no or minimal opioid use

   a. Defined as completing Month 3 and Month 6 visits with self-reported opioid use on ≤4 days in the past month and/or 2 or more consecutive negative urine tests.
2. The proportion of persons who remain HIV negative.
   a. Measured via negative HIV test at Month 3 and Month 6
3. Retention or persistence in care
   a. Defined as the proportion who remain on treatment (MOUD, PrEP or both) at Month 3 and Month 6
   b. We will also examine whether participants are more apt to remain on paired/combined therapy compared to individual treatment.

7. Reimbursement

Medical care and medications are being provided free of charge and participants will be provided with bus passes to cover all visits to the SSP (weekly for Month 1 and then monthly until end of study) and to the pharmacy. Participants will be offered additional bus passes for unscheduled visits if needed.

Description of Potential Risks

The study will provide MOUD with bup/nx and a prescription for PrEP for 6 months. At the end of study, all participants will be linked with local MOUD and PrEP clinics in Charlotte to ensure continuity of care. These clinics will be identified early in the study. If participants are leaving the area, assistance will be given to locate an appropriate clinic.

Bup/nx: If participants are not in withdrawal at time of induction, bup/nx can precipitate withdrawal. There is also the risk of overdose, misuse and abuse, especially if participants are using concomitant benzodiazepines and other central nervous system depressants, including alcohol. These risks and side effects will be discussed with participants and a handout detailing these adverse effects will be provided. Additionally, participants will be encouraged to keep the medication in secure storage and out of sight and reach of others, especially children.

There is also risk of abrupt discontinuation of bup/nx due to incarceration, loss of access, withdrawal from the study, noncompliance, or diversion.

Lab results including HIV/hepatitis: Participants may become worried or anxious when waiting for their test results. They will be informed that they can speak with the study provider/PI about their concerns if they wish.

Potential loss of confidentiality: Every effort will be made to protect participants' privacy and confidentiality; however, as with all research, there is no guarantee that privacy and confidentiality can be fully maintained. Therefore, there is the potential risk of loss of confidentiality.

If a participant indicates potential harm to self or others, this will need to be addressed appropriately and with sensitivity. Any disclosures will be handled within the framework of existing legal mandates, clinical practice, and social norms. When possible, disclosures will be discussed with the participant to determine the best management alternatives. This may include

notifying family members, referring to medical treatment, calling emergency services, or escorting the participant to a local hospital in Wilmington or Charlotte. When required by law, the Police Department and/or the Department of Social Services will be notified.

Anticipated Benefits

Participants are benefiting in that they will receive MOUD and PrEP at no cost, medications that have demonstrated efficacy for reducing opioid use and preventing HIV infection, respectively.

Confidentiality/Data Safety and Monitoring

We will have several procedures in place to protect participants' privacy and to keep their data confidential.

1. We will obtain a Certificate of Confidentiality (COC) from the National Institutes of Health so we are able to legally refuse to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings (IRB approval must first be granted before the NIH will issue a COC). We will not conduct any study procedures until the COC is obtained.

2. All research activities will be conducted in private locations.

3. Participants will be issued a Duke medical record number to be used on all study documents instead of participants' names.

4. All participant information will be stored within the Duke electronic medical record.

5. Participants will not be mentioned by name in any report or publication, nor will any information be included that could be easily traced back to an individual. All study results will be presented in aggregate.

6. Any electronic data files other than patient medical records will be stored in a folder on the secure Duke server

7. All hard copies of data generated during the study (handwritten notes, consent forms) will be stored in a locked cabinet within a locked office at the study site only accessible by the study team. Files will only remain at the study site until the study team can retrieve them and scan and upload them to create electronic copies. The paper copies will then be destroyed as per University guidelines.

8. All data will be stored securely at Duke University for up to 6 years after completion of the study.

8. Ethics

Ethics Training

Study staff will have completed all required research ethics training prior to contact with any participant or their data. Site coordinators will be fully trained in Duke Research Ethics training.

Study Monitoring

Standard operating protocols will be developed for each site. We will also be monitoring for bup/nx misuse and diversion via urine tox screens, although they will not be mandatory. Participants who test negative for bup/nx will not be taken off the study; rather, they will counseled on the importance and benefits for MOUD.

We will have weekly team meetings with each of the SSPs to ensure that we are on track. This will include reviewing enrollment and retention rates, and making adjustments as needed to ensure that the project objectives are being met.

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