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Design and implementation of a cohort study of persons living with HIV infection who are initiating medication treatment for opioid use disorder to evaluate HIV-1 persistence

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ABSTRACT

Background: Opioid use disorder (OUD) negatively impacts the HIV continuum of care for persons living with HIV (PLH). Medication treatment for OUD (MOUD) may have differential biological effects in individuals with HIV and OUD. To understand the role of MOUD – opioid agonist methadone, partial agonist buprenorphine and antagonist naltrexone – in HIV-1 persistence and reactivation, we will use molecular virology approaches to carry out the first prospective, longitudinal studies of adults living with HIV with OUD initiating MOUD. One of the major challenges to studying the impact of MOUD on HIV persistence is the low retention rate of study participants and the requirement of large-volume blood sampling to study the HIV proviral landscape and expression profiles.

Methods: A prospective cohort study is underway to study the HIV-1 expression, proviral landscape, and clonal expansion dynamics using limited blood sampling from persons with DSM-5 diagnosed OUD who are living with HIV infection and initiating treatment with methadone, buprenorphine, or extended-release naltrexone.

Results: We describe the recruitment, laboratory, and statistical methods of this study as well as the protocol details of this on-going study. Out of the 510 screened for enrollment into the study, 35 (7%) were eligible and 27 were enrolled thus far. Retention through month 3 has been high at 95%.

Conclusions: This on-going study is evaluating the impact of MOUD on HIV persistence at the molecular virology level using limited blood sampling via a prospective, longitudinal study of people living with HIV DSM-5 OUD initiating treatment with MOUD.

1. Introduction

Approximately there are 38 million people globally living with HIV as of 2019, of whom 1.2 million aged 13 and older are living in the United States (U.S.) [1]. While the overall U.S. HIV incidence remained stable in 2018 as compared with 2014, HIV diagnoses increased among people who inject drugs (PWID) [1] Globally, PWID accounted for an estimated 12% of global infections [2], and in the U.S. in 2018, of the 37,968 new HIV diagnoses, 7% were among PWID [1]. Due to the observed increases in PWID, there is a greater need for research investigating the intersection between risk for HIV and PWID, and in particular those with opioid use disorder (OUD).

HIV among PWID can be managed by the early and vigorous implementation of education, syringe service programs, and medication treatment for OUD (MOUD) [3]. FDA-approved forms of MOUD in the U.S. are: extended-release naltrexone (XR-NTX), an opioid antagonist; methadone, an opioid agonist; and buprenorphine, a partial opioid agonist. MOUD reduces HIV acquisition, drug overdose deaths, crime, and substance use among PWID [4,5] and improves HIV viral suppression in PLH with OUD [6,7].

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HIV persistence and reactivation is an ongoing battle between the clonally expansion of HIV-infected $CD4^+$ T lymphocytes [8–10] and elimination by immune effectors, such as cytotoxic T lymphocytes (CTLs) [11,12] and natural killer (NK) cells [13]. In animal studies, opioid use can impair immune effector cell function through μ opioid receptor, such as inhibiting T cell proliferation [14] and natural killer (NK) cell function [14,15], while μ opioid receptor antagonist naltrexone [14,16] or genetic knockout [17] can antagonize such immunosuppressive effect. The impact of opioid use and importantly MOUD on HIV persistence in PLH remains unknown.

A major challenge to understanding the impact of MOUD on HIV persistence in PLH is the requirement of an interventional clinical trial to study the impact in vivo. Ideally, such a clinical trial would require comparison of HIV persistence within the same individual before and after MOUD to reduce the impact of high individual differences and biological diversity on interpretation of results. Second, PLH and OUD typically have low retention rates in treatment [18], impacting a clinical study. Third, in order to evaluate the true size of HIV persistence in the latent reservoir, as opposed to labile forms of unintegrated HIV, the evaluation requires study participants to be virally suppressed for more than 6 months [19–21]. Lastly, such studies typically require large volumes of blood sampling requiring more invasive procedures such as leukapheresis [20,21] to characterize the rare HIV-infected cells (<1000 per million [<0.1%] $CD4^+$ T cells), or limit the laboratory analysis to a single assay [22].

Therefore, to understand the role of MOUD in HIV-1 persistence and reactivation, we designed the first prospective, longitudinal study of adults living with HIV and OUD who are initiating MOUD in the community with limited, non-invasive blood sampling (<100 ml per visit) for molecular profiling of the HIV latent reservoir. We describe the approach of this on-going study that is being undertaken to help evaluate how better HIV-1 cure strategies can be developed for PLH with OUD. In addition to addressing these biological questions, this cohort will also provide insights into persons with OUD and HIV who are actively seeking, initiating, and being retained on one of the three forms of FDA-approved MOUD.,

2. Methods

2.1. Study design

Project Persistence (Evaluating the role of medication treatments for OUD in HIV-1 Persistence for persons living with and OUD) is a NIDA-sponsored (R61/R33 DA047037) prospective cohort study conducted between December 2018–2021 of PLH and met DSM-5 criteria for moderate to severe OUD who are initiating MOUD (methadone, buprenorphine, or extended-release naltrexone) with community providers. We are obtaining whole blood samples following consent (Day 0) before MOUD is initiated, and at months 1 and 3 post-MOUD initiation. In addition to biological samples, all enrolled participants complete baseline assessments and follow-up interviews conducted at month 1 and month 3 time-points as delineated in Table 1.

2.2. Ethical oversight

Institutional Review Boards (IRB) at Yale University (HIC# 2000023013) and the Connecticut Department of Correction (CTDOC) reviewed and approved all study procedures. Additional protections were provided by the Office of Human Research Protections at the Department of Health and Human Services, and a Certificate of Confidentiality was obtained.

2.3. Research goals

The main aims of this research study are to determine if treatment with different forms of MOUD change: 1) HIV-1 expression, 2) the HIV-1 proviral landscape, and 3) the host genomic architecture. Ultimately, this study aims to use a comprehensive HIV-1 viral genomics and human genomics approach to carry out the first prospective, longitudinal study of PLH with OUD starting MOUD in order to understand how MOUD may change the viral and human genomic landscape, which will facilitate the development of a better HIV-1 cure strategies in PLH with OUD.

Table 1
Study activities and measures.

Study Activity	Study Time Point		
	Baseline	Month 1	Month 3
Screening for eligibility	X		
Consent	X		
Obtain or update locating information	X	X	X
Study blood sample	X	X	X
Research Interview:			
Demographic questions	X		
Housing Questions	X	X	X
Current and past medical history	X		
Current medications	X	X	X
HIV questions (medications, adherence, etc.)	X	X	X
MOUD questions (type, dose, changes, etc.)	X	X	X
Mental health diagnosis and treatment questions	X	X	X
Alcohol Use Disorders Identification Test (AUDIT)	X		
Addiction Severity Index (ASI) legal questions	X		
Alcohol, Smoking and Substance Involvement Screening Test (ASSIST v3.0)	X		X
Opioid Craving Scale	X	X	X
Patient Health Questionnaire (PHQ-9)	X	X	X
WHO Quality of Life-BREF (WHOQOL-BREF)	X	X	X
HIV Risk Behaviors	X	X	X
Mini International Neuropsychiatric Interview (MINI) v7.0.2	X		
Time Line Followback (TLFB)	X	X	X
Clinical Tests - on site:			
Rapid HIV test	X		
Rapid HCV test	X		
Urine toxicology screen	X	X	X
Pregnancy test	X	X	X
Breathalyzer	X	X	X
Clinical Lab Tests:			
HIV-1 RNA level*	X		X
CD4 count*	X		X
HCV RNA level§	X		X
Compensation for participation:			
Interview	X	X	X
Study blood sample	X	X	X

Abbreviations: MOUD = Medication for Opioid Use Disorder; HCV=Hepatitis C Virus.
*for those with HIV or positive rapid HIV test.
§for those with HCV or a positive rapid HCV test.

2.4. Sample size and power calculations

These analyses are intended to be exploratory and hypothesis-generating, therefore, sample size and power calculations were not conducted. We aim to enroll approximately 15 participants with complete samples at all study time points (baseline, months 1 and 3 post MOUD initiation), with a target of N = 5 participants per the three MOUD regimens. The next phase starting in year 2021 aims to enroll a total of 36 PLH and OUD initiating MOUD, with a target of N = 12 participants in each of the three MOUD groups. Although we will not be recruiting a large sample size, the anticipated enrollment will provide the information needed to generate parameter estimates and measure variable, as well as effect sizes. This will inform framing questions in the context of subsequent projects that will be powered to answer clinically important questions.

3. Study procedures

3.1. Recruitment and screening

The study began recruitment in December 2018. Participants who are to start MOUD at an approved study site are screened and enrolled the day they are to begin MOUD if found to be eligible. Approved study sites include: the APT Foundation, Yale Community Health Care Van, Nathan Smith Clinic, and the Substance Abuse Treatment Unit, a part of Addiction Services of the Connecticut Mental Health Center, in New Haven, CT; Connecticut Addiction Medicine in Harford CT; and facilities of the Connecticut Department of Corrections throughout CT. In 2021, the Denver Health and Hospital Authority Public Health Use Disorder clinic, in Denver, CO was added as a study site.

Screening questions to determine eligibility are incorporated into REDCap [23]. Those who meet study inclusion criteria are invited to participate in the study. Participants are asked to sign a medical release of information form to allow study staff to speak with MOUD providers to confirm MOUD initiation and retention.

3.2. Eligibility

Inclusion criteria include: 1) age 18 years or older; 2) able to speak English or Spanish; 3) meets DSM-5 criteria for moderate to severe opioid use disorder; OR if starting extended-release naltrexone for alcohol use disorder with a history of opioid use (use of illicit opioids [e.g., heroin or fentanyl] or prescription pain medication not as prescribed [e.g., Percocet, MSCONTIN, or oxycodone]); 4) able to give verbal and written informed consent; 5) receiving OUD treatment at an approved study site; 6) initiating methadone, buprenorphine, or extended-release naltrexone for opioid use disorder, OR starting extended-release naltrexone for alcohol use disorder and have a history of opioid use; 7) living with HIV and prescribed antiretroviral therapy (ART); and 8) be virally suppressed (HIV VL $<$ 200 copies/ml according to latest DHHS guidelines).

Exclusion criteria include: 1) Unable to give verbal and written informed consent, 2) suicidal ideation or plans for self-harm; 3) displays threatening behavior towards staff (clinic or research staff); 4 already maintained on a form of MAT; 5) pregnant or breastfeeding, not willing to use contraceptives; 6) self-report of fever in the past 2 weeks; 7) has an immunosuppressive condition other than HIV; and 8) Not virally suppressed (HIV VL $>$ 200 copies/mL).

3.3. Informed consent and enrollment

Participants undergo an informed consent process conducted by the research staff who assess willingness to participate in the study, including point-of-care testing for HIV and Hepatitis C infections upon enrollment and blood draws at each study visit. Research staff assures the participant's understanding of the study purpose, the details of study participation, and have all questions answered. If the participant agrees to participate in the study, they will be asked to sign the informed consent form (approved by the Yale IRB) and a release of information for medical and drug treatment information. After receiving written informed consent from the research participant, a research study staff collects detailed contact information from the research participant that includes their full name, aliases (if any), address, phone number, and information for alternative contact.

3.4. Baseline and follow-up visit procedures

All enrolled participants complete baseline assessments and blood draws of 70–80 cc for study analyses. Follow-up interviews and blood draws are conducted at each study visit at month 1 and month 3 after baseline. Please refer to Table 1 for the study activities, measures, and the study timeline.

Rapid HIV and HCV tests are administered to participants at the baseline visit. A rapid test for HIV (OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test) [24] and HCV test (OraQuick® HCV test) is performed on all consented participants by trained and certified research staff. For these tests, participants receive information on the procedure, meaning of test results, and an explanation of the window period during which an HIV antibody test might be negative [25]. A reactive HIV or HCV rapid test is followed by a confirmatory blood test conducted by Quest Diagnostics, using HIV and HCV viral load (VL) tests with detectable ranges of 20 copies/ml to 10,000,000 copies/ml and 15 IU/ml to 100,000,000 IU/ml, respectively. HIV VL and CD4 count will be obtained at baseline and months 1 and 3 as well.

Participants meet with study staff at each scheduled visit to complete the interview, phlebotomy, urine toxicology screens, urine pregnancy tests for child-bearing participants, and alcohol breathalyzer assessment (Alco-Sensor IV breathalyzer). Participants who stop MOUD or switch treatment are followed until the end of the study and receive the same assessments as other participants. Participants who return to substance use are referred to New Haven's syringe services program (or other local program), which provides safe injection equipment, naloxone, and has opioid and other substance use treatment programs.

3.5. COVID-19 considerations

Recruitment was temporarily paused from March 13, 2020 through June 22, 2020 due to the COVID-19 pandemic and resulting restrictions set by Yale University regarding ongoing research. During this time, follow-up interviews were completed with currently enrolled participants, but blood samples and urine toxicology were unable to be obtained. COVID-19 has substantially impacted access to MOUD, has increased overdose related deaths, and those who use substances are at high risk for hospitalization and death if they are infected with COVID-19 [26–29]. Therefore, a screening procedure was established prior to meeting with the participant and at the time of the study visit to assess for COVID-19 infection. These screening questions include current symptomology (including temperature checks at the time of visit), travel behaviors, and exposure to someone with active COVID-19 infection. Reported COVID-19 infections are noted in source documentation.

4. Covariate and outcome measures

4.1. Research assessments

4.1.1. Self-report measures

All study measures, outcomes, and overall timeline are depicted in Table 1. Self-reported measures from the research interviews including demographic information, housing status, current and past medical history, current medications, MOUD questions, and mental health diagnoses will be asked at baseline and throughout the study period. The Alcohol Use Disorders Identification Test [30] will assess for alcohol use disorder at baseline. The Addiction Severity Index [31] legal section of questions is used to assess participants involvement with the criminal justice system will be asked at all study interviews. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST v3.0)[32] assesses frequency of alcohol, tobacco, stimulants and other substances. The ASSIST is used to measure changes in potential substance use over time that may confound the final outcomes, specifically stimulants, cannabis, alcohol, and tobacco. Frequency and route of opioid use will be assessed using the Timeline Follow Back (TLFB) [33,34] during the past 90 days (baseline, day 0) and subsequently to assess opioid use reoccurrence outcomes at months 1 and 3. The Opioid Craving Scale [35] assess craving on a zero to ten scale, (rated from 'no craving' to 'I think about it all the time'). The Patient Health Questionnaire [36] is used to assess depressive symptoms. The WHO Quality of Life-BREF [37] is the abbreviated version of the WHOQIL-100, and will be used to assess quality of life around four domains (physical health, psychological

health, social relationships, and environment). The Mini International Neuropsychiatric Interview v7.0.2 [38] assesses for the 17 most common disorders in mental health including baseline substance use disorders. The current study also collects information on HIV sexual and injection drug use related risk behaviors, ART, and medication adherence. Data is collected using REDCap secure web-based application by research staff trained and certified in administering the interview tools.

4.1.2. Biological collection

A rapid test for HIV (OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test) [24] and HCV (OraQuick® HCV test) is collected at baseline. Confirmatory blood tests are conducted by Quest Diagnostics, using HIV and HCV VL tests with reportable ranges of 20 copies/ml to 10,000,000 copies/ml and 15 IU/ml to 100,000,000 IU/ml, respectively. Research staff were trained and certified in conducting the rapid HIV and HCV testing by the manufacturers. An 11-panel urine toxicology cup is used (Abbott®, formerly Redwood Toxicology) to test for cocaine, amphetamines, methamphetamine, methadone, opiates, oxycodone, phencyclidine, barbiturates, benzodiazepines, fentanyl, and buprenorphine at baseline and follow-up visits. Lastly, pregnancy tests are collected to confirm the pregnancy status of child-bearing participants.

4.2. Substance use outcomes and MOUD retention

The TLFB [33] asks about opioid use for every calendar day, and can be used to assess both prior and recent opioid use. Urine toxicology screens and the ASSIST [32] are conducted at all visits, asking about substance use and frequency of use. Variables that will be used to assess substance use include: 1) time to first opioid relapse, from the TLFB, 2) urine toxicology screen results, and 3) the ASSIST for substance and alcohol use in past 3 months. From the TLFB data, median time to relapse and Kaplan-Meier time-to-event analysis will be performed, and significance will be tested using log rank and Wilcoxon statistics. The number of days of opioid use per month will be calculated from baseline (30 days before enrollment) and for each time point. TLFB data will be compared to the urine screen toxicology results and responses from the ASSIST questionnaire. Participants are asked if they are still on the same form of MOUD as when they started the study to assess persistence on MOUD. If they are not, they are asked if they stopped MOUD altogether or switched MOUD, and reasons why. Self-reported time to discontinuation of MOUD will be confirmed through prescription refill data sources.

4.3. Whole blood samples

We are obtaining samples following consent (Day 0) before MOUD is initiated, and at months 1 and 3 post-MOUD initiation. The APT foundation starts MOUD (methadone and buprenorphine) on the day of request regardless of stage of opioid withdrawal and has a set 3-day induction procedure for both forms of MOUD; 50% of the 300 patients starting MOUD per month are naïve to MOUD. In addition to the same buprenorphine induction procedures used at the Substance Abuse Treatment Unit and the Community Health Care Van, they also start XR-NTX in those who have not used opioids in 5 days who meet criteria for DSM-5 OUD and it is administered differently as a once monthly injection (380 μg fixed dose). Each study recruitment site initiates and maintains participants based on the organization's policy. We are obtaining samples of whole blood (~80 ml) in CPT Vacutainer tubes to facilitate separation of peripheral blood mononuclear cells and plasma.

4.3.1. Biorepository

Whole blood samples are processed within the same day of venipuncture. After Ficoll density gradient centrifugation, plasma was snap frozen in 2 ml per tube. Peripheral blood mononuclear cells were viably frozen in 10% dimethyl sulfoxide in aliquots of 10 million cells per tube.

5. Compensation for research participation

Participants are compensated for their contribution to research activities. Participants are compensated with gift cards in the amount of $25 for each study interview and $25 for providing a blood sample for a total of $50 at each study visit, equaling a total of up to $150 by the end of month 3.

6. Analytic plan

6.1. HIV-1 viral genomics and human genomics outcomes

The primary study outcome is to examine HIV-1 expression, proviral landscape, and genomic architecture in response to different forms of MOUD. These studies are intended to be exploratory and hypothesis-generating, and stipulate validation of a hypothesis arising from this work. We will conduct exploratory and descriptive analyses, as well as effect size analyses.

If recruitment of this observational study in which the providers determine choice of MOUD exceeds planned enrollment, we will confirm that characteristics of participants stratified by MOUD agent are comparable using parametric and non-parametric tests as appropriate. If it appears as if there are no widespread systematic differences, we will calculate propensity scores (PS) [39] for MOUD treatment for all participants and use a matching algorithm [40], in concert with appropriate calipers, to match one reference participant to each patient receiving a specific MOUD. The use of PS matching combined with longitudinal immunologic markers will reduce the sources of confounding in inferring the relationship with MOUD. PS allow for the assessment of whether the characteristics of those receiving a specific MOUD agent overlap enough with those not being treated with that agent, thereby yielding an unbiased estimate of the treatment effect from the data. Given a collection of covariates that are thought to reasonably capture the significant predictors of treatment use, the treatment effect estimated from the difference of pairs of experimental units matched by PS [41] is more likely to be approximately unbiased. We will employ the method based on nearest available Mahalanobis metric matching within calipers defined by the PS. The Mahalanobis distance is used to identify the specific unit from the treatment arm whose covariate information is most similar within the framework of a range of PS values. An important consideration in the usage of a PS-based model is the choice of specific variables from which to calculate the PS. The choice of variables included can affect the bias, variance, and mean squared error of an estimated treatment effect derived from comparison groups constructed via PS methods. Using these PS-matched subjects, we will use multivariable non-linear mixed effects models [42] and test for the optimal covariance structure to capture within person correlation over time. Analyses will adjust for variables contributing to improved model fit, potentially including gender, race, type of MOUD, persistence on MOUD, co-occurring substance use disorders in addition to OUD (and substance use disorder severity), and comorbid medical conditions (including HCV). Dose ranges are specific to each of the MOUDs; therefore, dosage distribution will be assessed within each of the medications. These models will test whether type of MOUD (buprenorphine vs. methadone vs. XR-NTX) is associated with geonomic outcomes. Regression analyses [43] will include checks of model assumptions and goodness of fit using residual analyses, influence diagnostics, and goodness-of-fit statistics.

Methods of handling missing data [44] will test missing completely at random (MCAR), at random (MAR), or missing not at random (MNAR). The nonlinear longitudinal regression models are unbiased when data are MCAR or MAR. The SAS® v9.4 multiple imputation procedure now has a MNAR statement that imputes missing values by using the pattern-mixture model approach. To assess the MAR assumption, sensitivity analyses will compare models by varying the level of informative missingness. We will fit the validation cohort to

these regression models and will use both internal and external validation techniques to test reproducibility. Using jackknife methods [45], we will test whether ≥90% of observations fall within the confidence bands during internal validation. We will also perform external validation using a cohort of half of the participants and anticipate achieving 85% of observations falling within the original confidence bands for the validation cohort. Analyses will employ SAS v9.4, and a type I error of 5% (two-sided) will test for statistical significance. For exploratory hypothesis generation there will be no adjustment for multiple comparisons, but once the set of hypotheses are determined, the primary will be tested at type I error of 5% and the secondary hypotheses will maintain a family-wise type 1 error of 5% using the Hochberg multiple comparison correction [46].

7. Recruitment, retention and baseline characteristics

Of the 510 screened for eligibility thus far, 35 (~7%) were eligible for enrollment and 27 were fully enrolled. Reasons for ineligibility and refusal of study participation are detailed in Fig. 1.

Four participants were dis-enrolled for one of three reasons: not being virally suppressed, not having baseline blood draw, or they did not start MOUD. One participant died while on study and was dis-enrolled. Study visit retention has been 77% for month 1 and 77% for month 3. Retention on MOUD treatment for those who had an interview at each time point was 89% at month 1 and 72% at month 3.

Rapid HCV tests were completed for 7/27 (26%) participants; the remaining participants reported a prior HCV diagnosis. Of those tested, 3 had a preliminary positive HCV test and were referred for lab work and/or follow-up care. Those who completed a month 3 interview, all consented to HCV rapid tests, and no new HCV diagnosis were detected. Of those who have had follow-up interviews, we have obtained study samples from 90% of those who had a Month 1 interview and 100% at Month 3.

8. Discussion

This is the only study that we are aware of to date that is prospectively evaluating viral expression, proviral landscape, and human genomic architecture among persons with HIV with opioid use disorder initiating MOUD. At present, there are no validated guidelines for deciding the appropriate selection of MOUD, and this choice is largely dependent on clinical experience and practitioner preference. The potential biologic effects of MOUD agents on HIV latency, particularly relevant in PLH with OUD, remain incompletely studied. While this study is hypothesis generating, we will also test the hypothesis that methadone, buprenorphine, and XR-NTX will differentially affect the host genomic architecture. The findings from this study may show whether methadone, buprenorphine, or XR-NTX may be more suitable for persons with OUD based on HIV status and other factors.

Thus far, our recruitment of study participants has been consistent with our recruitment goals. However, the difficulty of finding PLH and OUD starting MOUD, especially XR-NTX, has been a challenge. The COVID-19 pandemic also contributed to a delay in recruitment for three months.

To date, interview retention has been good, with 77% of enrolled participants retained at month 3. This study's low attrition rate is outstanding given that this population faces unique challenges that make it difficult to stay engaged in both clinical care and research. Thus far, retention on MOUD treatment has shown 72% maintaining on any form of MOUD by the end of the 3-month follow-up period. Notably, this is greater than MOUD retention in other published MOUD studies [6,47]. However, results from this study may not be generalizable to persons starting MOUD outside of research settings, but instead to groups that remain maintained on MOUD. Reoccurrence to substance use has been shown in other studies to be common among persons with OUD [48,49], and could account for some instances of stopping MOUD in the current study. All participants who stopped MOUD were offered referrals to return to a treatment program.

All participants consented and agreed to have rapid HCV tests at baseline. Rapid HCV tests have been found to be widely accepted among young PWID due to the quick results, accuracy, and non-invasive methods [50]. Among participants there were several diagnoses of past or current HCV that warranted further testing. Injection drug use remains the leading behavioral risk factor for HCV infections [51], which makes frequent testing and treatment for both HCV and HIV critical among persons with substance use disorders, especially outside of research settings.

While engagement with MOUD can help reduce HIV and HCV acquisition, the current infrastructure for MOUD is insufficient to address the opioid epidemic, especially in rural areas. Ending the opioid and HIV epidemics will require actions taken by healthcare professionals, researchers, public health experts, policymakers, funders, and the public. The current project may help determine whether methadone, buprenorphine, or XR-NTX is a more suitable treatment for

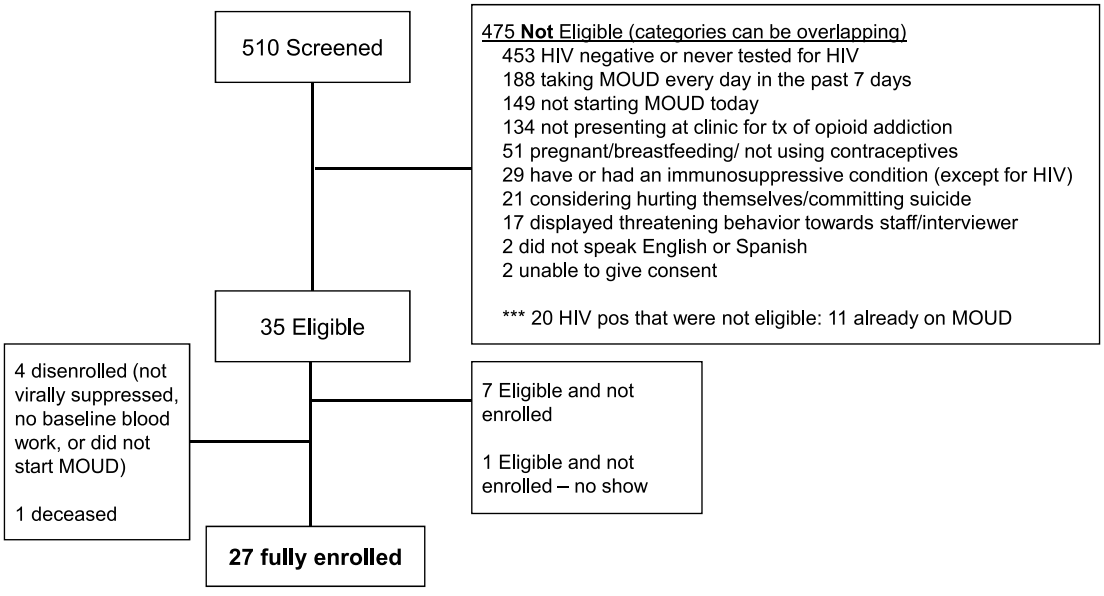

Fig. 1. Project persistence- study enrollment flow chart, through May 04, 2021.

OUD based on biologic effects and other factors and can help guide future research and protocols to better treat OUD. The increased use of fentanyl has contributed to the escalating mortality rate over the past 15 years [52,53]. Not only has there been an increase in mortality, but HIV outbreaks have occurred in places with no prior history, as well as places where HIV infections among PWID had been stable or decreasing [54,55]. Increases in novel HCV infections have coincided with increases in injection drug use [56,57]. Additionally, from 2014 to 2018 the number of diagnosed HIV infections attributed to injection substance use increased among male and female adults and adolescents [58]. Therefore, strategies that target MOUD, HIV, and HCV treatment could be vital to ending both the OUD and HIV epidemics.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Springer has received honoraria from Alkermes Inc and has received in-kind donations of extended-release naltrexone for prior and current NIH-sponsored trials ; and Indivior incorporated has provided in kind donations for Sublocade for this NIH-sponsored project.

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