Collaborating Consortium of Cohorts Producing NIDA Opportunities (C3PNO) COVID-19 Survey Protocol

Background: Description of Parent Grant

The Collaborating Consortium of Cohorts Producing NIDA Opportunities (C3PNO) (U24DA044554) brings together a diverse group of cohorts uniquely able to study the immediate and longitudinal impact of the COVID-19 epidemic and stay at home orders on the health and wellbeing of people living with HIV (PLWH) and substances use disorder (SUD) across North America. C3PNO was established in 2017 by the National Institute on Drug Abuse (NIDA) to enhance data sharing, encourage standardization of measurement and analysis tools, and facilitate collaborative research efforts among NIDA-supported cohorts that examine HIV/AIDS in the context of substance misuse. The consortium has a set of common data elements across cohorts and a curated dataset of measures of substance use, HIV, mental health, and behaviors as well as other salient clinical, laboratory markers collected every six months before the shutdowns in each cohort's location and continuing remotely as much as possible since the COVID-19 stay at home orders.

C3PNO includes nine NIDA cohorts with a combined sample size of approximately 10,000 active and 20,000 historical participants[1] spanning the U.S. and Canada including diverse high-risk HIV-negative and HIV-positive persons. The cohorts include: AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) (Vancouver, Canada); AIDS Linked to the Intravenous Experience (ALIVE) study (Baltimore, MD); the Heart Study (Baltimore, MD); the Healthy Young Men's (HYM) study (Los Angeles, CA); the Johns Hopkins HIV Clinical Care Cohort (JHHCC) (Baltimore, MD); the Miami Adult HIV Study (MASH) (Miami, FL); the MSM and Substances Cohort at UCLA Linking Infections Noting Effects (mSTUDY) (Los Angeles (L.A.), CA); the Multilevel Influences on HIV and Substance Use in YMSM Cohort (RADAR) (Chicago, IL); and the Vancouver Drug User Study (V-DUS) (Vancouver, Canada). Some cohorts exclusively enroll people who inject drugs (PWID) or HIV-Hepatitis C (HCV) positive or persons; eight cohorts have community-based research sites and one cohort is based in an HIV clinic. Many HIV-positive cohort participants are viremic and were struggling with sustaining care and controlling their HIV to achieve undetectable viral load (UVL) prior to the COVID-19 epidemic. The HIV-negative participants in the cohorts either historically enrolled PWID (ALIVE, Heart Study, V-DUS) or men who have sex with men (MSM) who use substances (HYM, mSTUDY, RADAR) all at high risk for HIV. Eight of the C3PNO cohorts participated in the administrative supplement with the Heart Study unable to join due to regulatory limitations.

We used both existing (prior to COVID-19 routinely collected) and newly collected data to address the aims of this study. Existing data will serve as the baseline before the COVID-19 epidemic and includes the battery of common data elements collected by each cohort with extensive information on sociodemographic characteristics, sexual risk behaviors, substance use behaviors, and HIV care and prevention. We implemented a new COVID-19 module to collect data elements specific to this study. The COVID-19 specific module was administered at two different time points, three months apart. This allowed us to measure changes across three time points: from baseline (i.e., existing data collected prior to outbreak), changes within the course of outbreak, and then as the epidemic recedes. We characterized the fast changing and dynamic stage of the outbreak on individuals with physical and social vulnerabilities resulting from substance use and/or HIV infection. Furthermore, repeated COVID-19 specific survey administration allowed us to capture data related to COVID-19 transmission risks, symptoms, and health outcomes for those presumptively positive.

Table 1. C3PNO Cohort Characteristics

Cohort	Year Est.	Site	Population	N in FU	Female (%)	Age (IQR)^	PLWH (%)**
ACCESS	2005	Vancouver	PLWH; PWID	1,187	35%	47 (40–54)	100%
ALIVE	1988	Baltimore	PWID	1,442	32%	55 (47 - 60)	29%
Heart	2016	Baltimore	AA PLWH	752	37%	55 (50-59)	100%
HYM	2015	L.A.	YMSM	452	0%	23 (21-24)	11%
JHHCC	1989	Baltimore	PLWH; PWID	3,227	39%	56 (50-61)	100%
MASH	2015	Miami	AA & Latino	1,345	42%	56 (51-61)	48%
mSTUDY	2013	L.A.	MSM	534	0%	32 (27-38)	50%
RADAR	2014	Chicago	YMSM	1,055	0%	22 (20-25)	20%
V-DUS	1996	Vancouver	PWID; SIY	2,338	34%	32 (25–48)	1%

IQR = Interquartile range; AA = African American; SIY = Street-involved youth; ^ Median age at last visit; ** Current HIV status

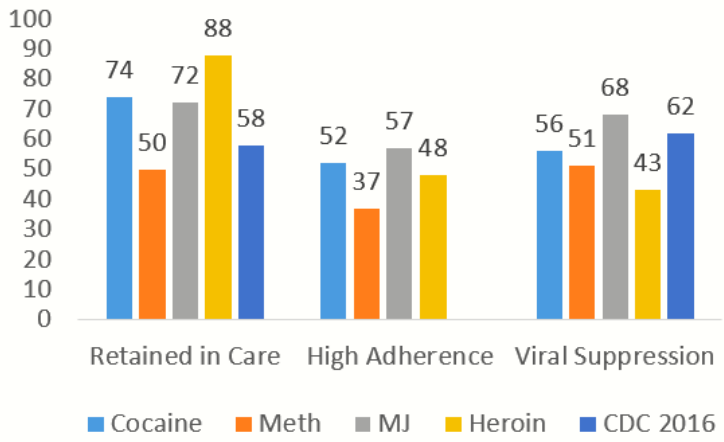
Approach

Study design and overview. C3PNO represents a rich resource to examine the effects of COVID-19. Common to all cohorts is a focus on the intersection of substance use and HIV. Most cohorts follow participants who are impacted by the ongoing opioid epidemic. Cohorts include participants with extensive experience with MOUD for heroin and with other treatment approaches for methamphetamine use. The cohorts have experienced recent resurgence of overdoses due to the introduction of fentanyl into these communities of injection drug users and where there is high risk of potential new outbreaks of HIV.[18] Substance use in the cohorts is a central focus of data collection, and the cohorts capture the heterogeneity in types of substances used by the cohorts, reflecting current or emerging trends in each cohort's unique setting. While heroin was the most commonly used drug among the first cohorts and remains prevalent, the recent explosive increase in exposure to synthetic opioids (e.g., fentanyl) is captured by the Vancouver cohorts (ACCESS and V-DUS), ALIVE, and JHHCC in Baltimore, and there is evidence it is increasing in Miami (MASH). Other opioid use such as non-medical use of prescription drugs is clearly evident as well with recent increases being seen in the cohorts. Finally, methamphetamine and other stimulant use is of high prevalence among the cohorts of YMSM – particularly the HIV-positive men in the mSTUDY cohort in L.A. The effects of COVID-19 stay at home orders on access to and use of these substances is unknown.

Preliminary studies. The cross-cohort data reveals that at last visit overall 39% (3790/9723) are HIV-positive. The self-reported substance use at last visit across cohorts was as follows: 30% (2572/6647) heroin or illicit (non-medical) prescription drugs; 30% (1771/5958) heroin injection; 15% (1327/8994) non-medical prescription drugs (opioids, etc); 44% (3783/8558) illicit stimulants including methamphetamine and cocaine; and 24% (1248/5204) injected these drugs. Ever overdosing was reported by 2085/3656 (57%). Among two cohorts screening urine for fentanyl exposure, 28% (712/2561) tested positive at the most recent visit. Most cohort members who reported ever injecting illicit substances are over 30 years of age and HIV-positive reflecting the cohort characteristics. Among PWID, heroin is the most common injected substance. In the last quarter of 2018, 2825 HIV-positive individuals completed a visit; of these, 62% had an undetectable viral load (HIV-1 RNA <20 copies/mL) with no difference by gender (p value=0.08). Viral suppression at last visit among heroin, cocaine/crack, prescription drugs, and methamphetamine users was 36%, 50%, 50%, and 56% respectively and lower than non-users of these substances (p value <.01 for all). Less than 100 participants across the cohorts reported use of any other drug types.[1]

Comparing how C3PNO users of different substances perform across the HIV Care Continuum reveals important differences by the drug used and where substance use treatment may make an impact (see Figure 1). Compared to CDC-reported retention of 58% in 2016, those reporting recent methamphetamine use in C3PNO had poorer retention in care (50%), whereas recent users of heroin, cocaine, or cannabis had higher retention compared to the CDC report (88%, 74%, 72% respectively). Compared to CDC-reported undetectable viral load of 62% in 2016, fewer C3PNO participants who reported recent heroin use (43%) recent methamphetamine use (50%) and cocaine use (56%) achieved viral suppression; but more were suppressed who reported recent cannabis use (68%). The same pattern was present for adherence – fewer C3PNO methamphetamine users had high adherence while a high percent of cannabis users had high adherence. These data indicate an urgent need for treatment of PLWH who abuse illicit substances before we can end the HIV epidemic.[19]

Figure 1: C3PNO HIV Care Continuum (HCC) % by Substance of Abuse



(CDC July 2019 Diagnosis Based HCC among people living with *diagnosed* HIV)

Recruitment and participant sampling. Participants included a minimum 200 participants from each of the participating C3PNO cohorts. Participants were eligible if: (1) they are enrolled in a C3PNO cohorts; (2) had a study visit in the last 12 months; (3) English or Spanish speaking; and (4) willing and able to complete data collection procedures proposed as part of this supplement. The minimum of 200 participants per cohort will result in an estimated minimum total sample of 1,400 participants. Additionally, this sampling strategy ensured that we have sufficient sample size across the various strata of interest including a sufficient sample of PLWH, those with SUD, and those with a history of injection drug use, and by key age groupings.

Study procedures. Each cohort identified/contacted potentially eligible participants already enrolled in their study. Each site will follow existing protocols and standard operating procedures for inclusion of their participants in remote visits and supplemental studies including consideration of relevant regulatory issues. The proposed study visit fell under the IRB protocol and informed consent for each existing cohort and may be conducted in conjunction with a (remote) routine visit. All participants in the proposed study will be informed that in addition to the first study visit, they will be contacted in again in three months in order to repeat the study questionnaire. These second visits would be considered as ancillary visits to the regular cohort scheduled visit which occur semi-annually. These will be either self-administered via a smartphone/computer or by telephone interview with the interviewer entering the data in the web-based questionnaire. Compensation will be provided for each survey.

Data collection and measurements. We used both existing routine and newly collected data to address the aims of this study. Existing data will serve as the baseline before the COVID-19 epidemic and includes the extensive battery of common data elements currently being collected as part of cohort participation with extensive information on sociodemographic characteristics, sexual risk behaviors, substance using behaviors, and HIV care and prevention. The COVID-19 specific questions were administered at two different time points, three months apart. This will allow us to measure changes across three time points: from baseline (i.e., existing data collected prior to outbreak), within the course of outbreak, and as the epidemic recedes. This will capture the fast changing and dynamic stage of the outbreak on individuals with physical and social vulnerabilities resulting from substance use and HIV infection. Furthermore, the repeated COVID-19 specific survey allowed us to capture data related to COVID-19 transmission risks, symptoms, and health outcomes for those presumptively positive.

Analytic strategy. Baseline data for the proposed study will include existing data collected at last visit by each of the cohorts. Changes to be analyzed across assessment include substance use including initiation (i.e., incidence) of different substances, prevalence, transitions between drugs, and frequency of use. We will also analyze changes in substance use disorder treatment including temporary disruptions or discontinuation; engagement in HIV prevention and care including changes in PrEP use (for HIV-negatives), access and adherence to HIV care appointments and adherence to ART for PLWH. For our Aim 2 we will estimate the proportion of people in cohorts who had confirmed COVID-19, confirmed or probable COVID-19, and proportion hospitalized. We will assess differences in substance using behaviors including type of substance (e.g. opioids, tobacco, cannabis, methamphetamine) and mode of use (e.g., smoking, vaping, injection) between those who were confirmed/probable cases of COVID-19 (based on self-report in the questionnaire or medical record) to those who were presumed not infected (i.e., not a confirmed/probable case). For our Aim 3 with our consortium cohorts we will assess how PLWH, those at high risk for HIV, and those who misuse substances experiences in and responses to the COVID-19 epidemic differ by assessing their ability and compliance with social distancing and hygiene guidance, and their approaches to managing basic living conditions during the stay at home orders and after.

Descriptive statistics, including mean, median, range, and frequency distributions will be calculated at baseline and differences between groups of interest will be evaluated using t-tests, chi-square methods, and Fisher's exact test, as appropriate. Differences in changes over time will be assessed using McNemar's test. For time varying factors (e.g., substance use) the descriptive statistics will be calculated for each time point (baseline, 12, and 24 weeks) and by HIV status and SUD status. Missingness will be assessed at each time point and if needed we will leverage our existing work and validated techniques for data linking, harmonization to conduct our analysis minimizing bias and variability. These techniques include use of multiple imputation and data linking using item response theory. We have developed a practical application for the evaluation of several imputation strategies and helps to address missing data problem in survey research in particular longitudinal studies.

Furthermore, changes in time-varying factors will be analyzed using either survival analysis or repeated measure strategies accounting for the repeated nature of the data and the within person effects. In order to assess factors associated with our main outcomes of interest (e.g., substance use initiation, non-adherence with HIV care) we will use generalized liner mixed models for categorical measures. We will fit models with random subject-specific intercepts and time effects to appropriately model the repeated measurements from each participant and allow participant-specific changes in the responses over time.

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