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Hepatitis C and HIV Treatment among Patients on Medication for Opioid Use Disorder (MOUD)

A dissertation submitted in partial satisfaction of the requirements

for the degree Doctor of Philosophy

in Epidemiology

by

Catherine Psaras

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ABSTRACT OF THE DISSERTATION

Hepatitis C and HIV Treatment among Patients on Medication for Opioid Use Disorder (MOUD)

by

Catherine Psaras

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2024

Professor Marissa J. Seamans, Chair

Opioid use disorder (OUD), hepatitis C (HCV), and HIV are components of a syndemic and public health emergency in the US. Effective treatments exist for all three conditions, but adherence to these treatments can be difficult, particularly for those with OUD. Evidence from real world data is lacking on the complex interactions between treatment for OUD and infections such as HIV and HCV. The studies within this dissertation investigate factors related to medication adherence among patients living with OUD and HCV or HIV using real-world data from a large administrative claims database of privately and publicly insured people. The goal of

this dissertation was three-fold. First, we described demographic, pharmaceutical, HCV treatment adherence, and healthcare utilization characteristics of those using both opioid agonist therapy (OAT), a treatment for OUD, and direct acting-antivirals (DAA) for the treatment of HCV (Aim 1). Second, we compared the effects of co-prescription of buprenorphine, a form of OAT, and ART protease inhibitors (PIs) on buprenorphine adherence (Aim 2). Lastly, using growth mixture modeling, we identified OAT long-term adherence trajectories and analyzed the predictors of OAT long-term adherence patterns (Aim 3). All aims were completed using a large administrative claims database of publicly and privately insured people in the US between 2015-2019.

Aim 1 was completed using a retrospective cohort of over 2,000 insured adults on OAT who initiated HCV DAA therapy between 2015 and 2019. Over time, the median age of cohort entrants decreased (2015: 49 (interquartile range (IQR): 30-57); 2019: 37 (IQR:31-46)), the prevalence of additional substance use diagnoses at baseline increased (2015: 58%; 2019: 70%), and the cohort transitioned from mostly initiating ledipasvir/sofosbuvir (proprietary name: Harvoni) in 2015 (59%) to mostly initiating glecaprevir/pibrentasvir (proprietary name: Mavyret) by 2019 (77%). Among the youngest cohort entrants (18-35 years old), 13% discontinued HCV DAA therapy early. Among the oldest cohort entrants (51-64), 9% discontinued early. Twelve percent of people with an additional substance use diagnosis at baseline discontinued their HCV DAA therapy early. In contrast, 10% of people with OUD alone discontinued their HCV DAA therapy early. These proportions remained similar regardless of commercial or Medicaid insurance source. Despite having high levels of potential risk factors for early discontinuation such as psychiatric comorbidity and substance use, the overall proportion of people who discontinued HCV DAA therapy before eight weeks was like that observed in populations

without OUD. This suggests that OUD should not be used as exclusionary criterion for payer authorization of these life-saving medications.

Aim 2 used a cohort of 255 people living with and receiving pharmacotherapy for HIV and OUD. There were small to no marked differences in buprenorphine adherence and persistence across protease inhibitor vs. non-protease inhibitor forms of ART. These results remained the same in the crude, adjusted, and sensitivity analyses. Future quantitative bias analysis can illuminate the level of misclassification needed on factors such as IDU, cocaine use, and psychiatric disorders to meaningfully change confounding control and thus the results of the present study. Future studies with a larger sample size can stratify analysis by the type of PI to avoid collapsing all PIs into a single category. Collapsing all PIs may have drowned the effects of potent PI-induced enzyme inhibition among PIs with weaker enzyme inhibition potential in our study.

For Aim 3, we identified three well-separated OAT adherence trajectories among 5,495 people living with HCV and OUD. We also examined the extent to which baseline demographic, clinical, and healthcare utilization characteristics predicted OAT adherence trajectory membership. Notably, 60% of the cohort was classified into sub-therapeutic adherence groups. Both the low and moderate OAT adherence trajectory groups had a mean proportion of days covered per month of less than 50% (<15 days). Additionally, we found that at baseline, having OUD without additional substance use diagnoses, initiating buprenorphine instead of methadone, older age, being female, a greater number of outpatient visits, and no overdoses were reliably associated with higher adherence during follow-up. Conversely, black race was associated with low adherence group membership.

The findings of this dissertation can be used to improve clinical guidelines for HIV treatment choice among those with OUD and help to target additional support for patients at increased risk of treatment non-adherence among people with OUD and HCV. Our results provide vital and novel information on strategies to address the public health emergency that is the OUD, HCV, and HIV syndemic.

The dissertation of Catherine Psaras is approved.

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Chapter 1 Introduction

Opioid Use Disorder (OUD) and Medication for Opioid Use Disorder (MOUD)

Opioid misuse and dependence are a public health emergency in the United States. Opioid use disorder (OUD) is a complex condition characterized by compulsive use of opioid drugs, despite a person's desire to stop or the negative impacts on their physical or emotional well-being.[1] OUD is increasingly common in the United States,[2] with around 2 million adults and adolescents twelve years and older diagnosed with OUD in 2020.[2,3] OUD, hepatis C (HCV), and HIV are components of a syndemic in the US.[4] Opioid misuse and injection drug use greatly increase the risk of HCV and HIV infection and transmission.[5] Crucially, HCV elimination and ending the HIV epidemic in the US will not occur unless the complex interactions between HIV, HCV, OUD and their treatments are comprehensively researched and addressed.[6,7]

Medication for opioid use disorder (MOUD) is the gold-standard treatment for OUD, and opioid agonist therapy (OAT) is the most common and efficacious form of MOUD.[8] The two OAT active ingredients approved in the US are methadone and buprenorphine. Both medications are synthetic opioids and are controlled by the US Drug Enforcement Agency. Buprenorphine is a schedule III narcotic analgesic, and methadone is a schedule II narcotic analgesic. These medications replace other opioids like fentanyl, heroin, and Oxycontin at the brain's opioid receptors. This prevents the harmful effects of opioid withdrawal and cravings without providing the dopamine-fueled euphoria that often leads to addictive behavior.[9] Despite the potential of OAT efficacy, 64% of people on MOUD treatment stop before six months.8 Treatment that lasts at least fifteen months is associated with significantly less hospital use, fewer overdose events,

and lower rates of prescription opioid use.[10] Addressing treatment adherence is important because short-term treatment is unlikely to provide lasting benefit to patients.

HIV Among People Living with Opioid Use Disorder

Certain populations, such as individuals with opioid use disorder and people who inject drugs (PWID), face heightened vulnerability to HIV infection compared to those without these substance use conditions. In 2020, there were over 30,000 new HIV cases.[11] Of the new cases, 7% were among PWID. Injection drug use alone is linked to delayed initiation of HIV treatment and reduced likelihood of HIV virological suppression.[12,13] However, among PWID, opioid agonist therapy receipt and adherence in comparison to treatment without OAT or non-adherence to OAT, has been associated with increased ART uptake,[14,15] adherence,[16,17] and viral suppression.[15,18,19] Buprenorphine initiation and adherence in comparison to no initiation or lack of adherence, regardless of injection drug use, was associated with increased ART uptake,[20] increased ART adherence,[21] and increased HIV viral suppression.[19,20]

The gold standard treatment for HIV, is antiretroviral therapy (ART). Some forms of ART are metabolized by the CYP3A4 hepatic enzyme, which also is involved in OAT medication metabolism. CYP3A4 also metabolizes numerous other medications and supplements. These include but are not limited to clarithromycin (antibiotic), erythromycin (antibiotic), diltiazem (antihypertensive), itraconazole (antifungal), ketoconazole (antifungal), verapamil (antihypertensive), goldenseal (dietary supplement), and grapefruit.19 One group of ART medications is called protease inhibitors (PIs). PIs are mainly metabolized by cytochrome P450 enzyme system, of which CYP3A4 is a member. Protease inhibitors also inhibit CYP3A4 activity within the body by irreversibly inactivating the enzyme.[22] This increases the plasma concentration of other drugs predominantly metabolized by CYP3A4. Inhibiting the activity of

the CYP3A4 enzyme may lead to lower than expected metabolism rates for buprenorphine and methadone. This would lead to higher concentrations in the blood plasma and potential unexpected treatment outcomes. For example, lower doses of buprenorphine may suffice if individuals taking protease inhibitors (PI) for HIV treatment experience increased blood concentrations of buprenorphine at the same dose. Protease inhibitors are generally one component of ART. PIs, such as ritonavir and lopinavir, block protease enzymes, which prevents HIV from becoming a mature virus that can infect other immune cells.[23] Understanding these mechanisms and enzymes can help illuminate other medications that may interact with HIV ART treatments. The social, geographic, and behavioral interactions of HIV ART and MOUD have been previously explored in epidemiologic studies, but biological/pharmacokinetic interaction processes have not.

Hepatitis C Among People Living with Opioid Use Disorder

People living with opioid use disorder and people who inject drugs (PWID) are at an increased risk for hepatitis C virus (HCV) infection, similar to HIV.[5] In 2020, the CDC reported that the majority of HCV incidence (66%) in the US occurred because of injection drug use.[5] Curative treatment for HCV has been available in the US since 2013. HCV treatment uses direct-acting antiviral (DAA) medications administered orally in the outpatient setting. Treatment is well-tolerated, highly effective (90% infection clearance), and generally lasts 8-12 weeks, depending on the type of HCV infection, extent of liver damage, and previous HCV treatment history.[24] Prior to the release of DAA treatments for HCV, interferon-based treatments were used. However, interferon treatments were complicated, less effective, generally completed at specialty clinics or hospital-based care, required regular monitoring, and were associated with numerous adverse effects.[25] The transformative shift from interferon-based treatments to DAA

therapies not only improved the effectiveness and accessibility of HCV treatment but also contributed to broader positive outcomes, such as decreased high-risk injection practices, decreased substance use, and increased housing, employment, and education opportunities.[25].[26] Treating HCV and OUD in tandem among PWID may improve engagement in care.[27] One program at the University of Maryland found that those who started buprenorphine at the same time as HCV treatment, had significantly better HCV cure rates, greater declines in opioid use, fewer overdoses during the study, and reductions in high HIV risk behaviors.[27,28] The impact of successful OUD and HCV treatment extends beyond viral clearance. Positive outcomes such as decreased high-risk injection practices, decreased substance use, and better housing, employment, and education opportunities have been observed.[25] In addition, people living with HCV on OAT also demonstrate a 50% reduction in HCV transmission.[29]

Objectives of this Dissertation

These three studies all investigate factors influencing medication adherence among patients with OUD, HCV, and HIV. The first study focuses on the characteristics of people who are adherent to HCV DAA among people on OAT, the second on the effect of co-prescribed HIV ART medications on OUD treatment, and the third on OAT adherence among those with HCV. This research aims to improve medication adherence programs for these complex patient populations.

Specific Aims

Aim 1

Previous research on patients prescribed both medication for opioid use disorder (MOUD) and HCV DAA therapy is limited. Earlier studies examining patients prescribed both HCV DAA therapy and medication for opioid use disorder (MOUD) [30,31] have generally been limited to clinical trial cohorts, data from specific clinics or cities, or broadly patients with one or more

substance use disorders. None have examined the characteristics of people prescribed both HCV DAA therapy and opioid agonist therapy using real-world data. This study investigates a broader range of patients to better understand early HCV DAA discontinuation. Understanding patterns of DAA discontinuation in real-world settings is crucial because adherence to HCV therapy may be lower in non-controlled settings than in clinical trials or prospective cohorts.[32]

Aim 1: The objective of this study is to describe the sociodemographic and clinical characteristics of people in the United States who have commercial or public insurance coverage between January 1, 2015, and December 31, 2019, who initiate HCV DAA therapy and medication for opioid use disorder (MOUD), estimate the frequency of HCV DAA early discontinuation, and to identify correlates of early discontinuation.

Aim 2

Pharmacokinetic studies have suggested that both methadone and buprenorphine use in the presence of a protease inhibitor for HIV treatment may lead to suboptimal levels of methadone and buprenorphine in the body, which require dose adjustments. When these interactions occur, it can make finding adequate and safe opioid agonist therapy dosing strategies for patients more complex.

Aim 2: The objective of this study was to examine the effects of co-prescription of ART PIs on buprenorphine treatment adherence among patients living with HIV and OUD using a large administrative database.

Hypothesis 1: OAT days will differ meaningfully between those on a PI form of ART and those on a non-PI form of ART after accounting for confounding factors.

Hypothesis 2: The length of time between initiation and discontinuation of OAT treatment (i.e., OAT persistence) will differ meaningfully between those who are on a PI or NNRTI form of

ART and those who are on a non-PI or NNRTI form of ART after accounting for confounding factors.

Aim 3

Effectively treating patients with HCV and OUD for both conditions is a public health imperative. People living with HCV and OUD, in comparison to OUD alone, have increased mortality and significant morbidity,[33] and people living with HCV on opioid agonist therapy (OAT) demonstrate a significant reduction in HCV transmission.[29] Thus, ensuring adequate access and adherence to agonist therapy is vital to reaching HCV elimination.[34] Previous studies examining OAT adherence using real-world data have not focused on people living with HCV. It is possible that living with HCV modifies the relationships between baseline patient characteristics and OAT adherence. Understanding patient characteristics related to OAT adherence among people living with HCV is vital to developing strategies to improve patient outcomes.

Aim 3: To identify adherence trajectories to OAT over 15 months following OAT initiation among people living with HCV using latent class growth analysis and to investigate baseline demographic, clinical, and healthcare utilization factors associated with distinct OAT adherence trajectories.

Data Source

Level of Information and Providers of Information

The analyses for this dissertation will use the IBM MarketScan Research databases. The MarketScan Research databases contain individual-level paid claims data that is longitudinal and linkable between service types and across different health providers and health plans. Individuals' health claims can be tracked across years and service types. Across the six available

databases, there are twenty billion service records. The analyses for this dissertation will contain data from two of the available six databases— MarketScan Commercial Claims and Encounters (CCE) data and the MarketScan Multi-state Medicaid database. Three-hundred fifty payers provide the data for these databases. This group is made up of large employers, health plans, and government/public organizations.

Types of Data

The Merative MarketScan databases contain multiple types of clinical and insurance data. These include but are not limited to enrollment information across services and clinical utilization. Enrollment information includes demographics, dates of enrollment from which one can deduce periods of continuous enrollment, the types of plans individuals were on for certain periods, and information on prescription drug coverage. Clinical utilization data come from both inpatient and outpatient records. Inpatient records include medical/surgical information. These medical and surgical procedures are identified by Current Procedural Terminology (CPT®) codes and have diagnosis codes associated with each procedure. Each encounter can have up to four principal CPT and diagnosis codes. Fourteen additional diagnosis codes for a total of eighteen can be added for each encounter. Diagnosis codes are in International Classification of Diseases (ICD) code format. Diagnosis codes before September 30, 2015, are in the Ninth Revision (ICD-9) format. After this date, they are in the Tenth Revision (ICD-10) format. All services from the same inpatient hospital admission can be linked using a case ID (CASEID). Outpatient records contain data on encounters/claims for services provided in doctors' offices and hospital outpatient facilities. Outpatient information also includes outpatient prescription information if the individual has prescription drug coverage through their insurance plan. These prescription drug claims can originate from mail-order or retail prescription drug providers.

Who is Captured?

Claims in the commercial database (CCE) and Multi-State Medicaid data draw from extensive sources including commercial insurance companies like Blue Cross Blue Shield and Medicaid programs spanning multiple states. Commercial data sources include claims information from active employees and their dependents, early retiree employees with company provided supplements, and Consolidated Omnibus Budget Reconciliation Act (COBRA) employees. The Multi-State Medicaid data includes data from seven million Medicaid recipients in eleven state Medicaid programs and Medicaid Managed Care programs.

Data Quality

IBM MarketScan has validated data contained in the CCE and Multi-State Medicaid databases. The distribution of categorical fields is compared to a norm. Diagnosis and procedural codes, dates of service, sex, and age are compared to lists of possible values. If improper coding is found, these observations are flagged and sent to payers as part of quality control improvement recommendations. MarketScan also tries to screen for duplicate records added to the payer system because of overpayments.

Benefits and Limitations of Using MarketScan Claims Data

Claims data have advantages over Electronic Health Record (EHR) data and data collected during observational and/or interventional research studies. First and foremost, the MarketScan claims databases contain billions of service records spanning millions of patients in the United States. This provides ample opportunity to capture populations, such as populations living with co-infection, that any one source would be challenged to provide sufficient sample size. Second, using claims data for pharmacoepidemiology research allows analyses to be limited to those individuals who filled prescriptions, not just those to whom a medication was prescribed. This is

not universally available in EHR systems. Third, claims data provide data on all health claims an individual has incurred through a year, not just claims limited to a specific clinic, healthcare system, or specific therapeutic area as would be available from other sources. This provides rich longitudinal data on patient populations that frequently change providers and healthcare facilities.

There are two notable limitations of this data. The main limitation of MarketScan data is their non-random nature—MarketScan data are not a random sample of insured individuals in the United States, but rather a large convenience sample. Commercial data are primarily from large employers and under-represent medium and small firms. In addition, the Medicaid data is provided from eleven states, which were not necessarily collected to be representative of the entire US Medicaid population. The second limitation is that geographic variables are missing from Medicaid data, while race variables are missing from commercial data. This limits analysis of geography and race to the commercial and Medicaid datasets, respectively.

Chapter 2 Hepatitis C Direct-Acting Antivirals: Description of Demographic, Insurance Coverage, Clinical Characteristics, and Early Discontinuation Among Insured Adults Receiving Treatment for Opioid Use Disorder and HCV (Aim 1)

Introduction

People living with opioid use disorder and people who inject drugs (PWID) are at an increased risk for hepatitis C virus (HCV) infection.[5] In 2020, the CDC reported that the majority of new HCV cases (66%) in the US occurred because of injection drug use.[5] Curative treatment for HCV using direct-acting antiviral (DAA) medications has been available in the US since 2013. Treatment is administered orally in the outpatient setting and generally lasts 8-12 weeks, depending on the type of HCV infection, extent of liver damage, and previous HCV treatment history.[24] Because treatment is well-tolerated and highly effective (>90% infection clearance),[35–38] maximizing HCV DAA adherence is an important public health strategy to eliminate Hepatitis C in the United States.

Previous research on patients prescribed both medication for opioid use disorder (MOUD) and HCV DAA therapy is limited. Broadly, women, young people, mental health comorbidity, publicly insured people, ribavirin therapy use, and cirrhosis at baseline have been associated with early HCV DAA early discontinuation among people with co-occurring substance use or MOUD therapy. [30,31,39–41] These earlier studies examining patients prescribed both HCV DAA therapy and medication for opioid use disorder (MOUD) have generally been limited to clinical trial cohorts, data from specific clinics or cities, or broadly patients with one or more substance use disorders. [30,31] None have examined the characteristics of people prescribed both HCV DAA therapy and opioid agonist therapy using real-world data. This study investigates a broader range of patients to get a better understanding of early HCV DAA discontinuation. Understanding patterns of DAA discontinuation in real-world settings is crucial because adherence to HCV

therapy may be lower in outside of research settings in comparison to clinical trials or prospective cohorts.[32]

The objective of this study is to describe the sociodemographic and clinical characteristics of people in the United States who have commercial or public insurance coverage between January 1, 2015, and December 31, 2019, who initiate HCV DAA therapy and medication for opioid use disorder (MOUD), estimate the frequency of HCV DAA early discontinuation, and to identify correlates of early discontinuation.

Methods

Data and Study Design

This was a retrospective cohort study utilizing the Meritave MarketScan Commercial and Multi-State Medicaid databases from January 1, 2015, through December 31, 2019. The MarketScan Commercial and Multi-State Medicaid databases contain information on individual-level paid claims that is longitudinal and linkable between service types and across different health providers and health plans. Claims in the commercial database (CCE) are populated from commercial insurance companies with broad geographic coverage.[42] The Multi-State Medicaid data includes data from seven million Medicaid recipients in eleven state Medicaid programs and Medicaid Managed Care programs.[42]

Inclusion/Exclusion Criteria

We included adults (≥18 years old) with OUD who initiated Hepatitis C (HCV) direct acting antiviral (DAA) medication and had at least one outpatient pharmacy prescription claim for opioid agonist therapy (OAT) in the 180 days before HCV DAA initiation. HCV DAA

medications were identified from outpatient pharmacy drug dispensing claims searching the generic names daclatasvir, dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, simprevir, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilprevir. The HCV DAA initiation date was considered the cohort entry date (Index Date). People without continuous insurance enrollment with prescription drug coverage for six months before the index date were excluded. The purpose of this exclusion was to ensure sure that all included people have a six month washout period prior to the first appearance of a HCV DAA outpatient prescription fill, to define incident use, and to allow adequate time to gather baseline covariate information. To examine early HCV DAA discontinuation, people without at least seventy days of continuous enrollment post-HCV DAA initiation were excluded. Seventy days post HCV DAA initiation was used because the minimum expected length of complete treatment for HCV DAA medication is eight weeks (8 weeks + 2 weeks grace period= 70 days).[43] Opioid use disorder was identified using ICD-9 and ICD-10 diagnosis codes and an algorithm described previously.[44] Inclusion was limited to people with a probable OUD diagnosis because opioid agonist therapy can be used for the treatment of moderate to severe chronic pain that requires pharmacotherapy treatment for extended periods of time. The end of follow-up was defined as the end of insurance coverage, prescription drug coverage, or the end of the study data (December 31, 2019).

HCV DAA Early Discontinuation

Duration of HCV DAA treatment was defined as the length of time from medication initiation (index date) to the end of the continuous use period. The end of the continuous use period was identified as an HCV DAA medication prescription without a refill within fourteen days of the

end of medication supply. Fourteen days was used as a grace period for prescription refill. Early discontinuation was defined as continuous use less than eight weeks.

Descriptors

Characteristics of cohort members were collected from inpatient and outpatient services and outpatient drug claims for reimbursed, dispensed prescriptions fills. Demographics, including age and sex, were gathered from the index HCV DAA prescription drug claim. Age was further categorized into three groups: 18-35 year-olds, 36-50 year-olds, 51-64 year olds. Information on advanced liver disease, cirrhosis, depression, anxiety, opioid overdose, and substance use other than opioids (alcohol, cannabis, cocaine, other psychoactive substances, and other stimulants) were extracted. Type of opioid agonist therapy was gathered from all claims during the six-month period before cohort entry.

Statistical Analyses

Baseline characteristics were summarized as median and inter quartile ranges (IQR) for continuous measures and frequency (%) by year of cohort entry and discontinuation status.[45] Additional substance use was examined by year of cohort entry and was the prevalence of each additional substance use diagnosis was age and sex adjusted. To identify baseline correlates of early HCV DAA early discontinuation during follow-up, marginal structural models (MSMs) using inverse probability of treatment weighting (IPTW) were fit to estimate marginal adjusted differences in risk of HCV DAA discontinuation between levels of baseline variables. Covariates used for adjustment in models were selected a priori based on background knowledge (Appendix Figures S1-6). Briefly, treatment models using logistic regression were constructed to estimate the probability of observed treatment (i.e., exposure level to the variable of interest) given

subjects' observed a priori selected covariates. Observations were then weighted by the inverse of their probability of treatment to construct pseudo-populations that were balanced on the selected covariates between the exposed and unexposed groups.[46] Using the weights, we then implemented linear risk models to estimate adjusted marginal risk differences. MSMs and a priori covariate selection were used to avoid common pitfalls of exposure-wide studies such as conditioning on possible colliders and mediators.[47] Models were then stratified by insurance type. In models where we examined associations between types of HCV DAA medications and early DAA discontinuation, we limited analysis to the three most common medications (glecaprevir/pibrentasvir (Mavyret), ledipasvir / sofosbuvir (Harvoni), and sofosbuvir/velpatasvir (Epclusa)) to avoid small cells sizes. Because glecaprevir/pibrentasvir (Mavyret) was approved in August 2017 and there were meaningful differences in DAA discontinuation by DAA type among Medicaid enrollees, as a sensitivity analysis, we repeated this analysis but limited inclusion to Medicaid enrollees who initiated HCV DAA therapy after September 1, 2017. Thus this limited analysis to only people eligible to be prescribed glecaprevir/pibrentasvir (Mavyret).[48]

This study was reviewed by the University of California, Los Angeles (UCLA) Institutional Review Board and deemed not human subjects research. All analyses were completed in Stata 16.1[49].

Results

We identified 2,935 patients with OUD who initiated use of HCV DAA during the study period (Appendix Figure S7). The present cohort skewed younger (median age: 38 (IQR: 31-52)) and had approximately equal proportions of males and females (males: 52%, females: 48%). Most

cohort members had Medicaid insurance (72%). Few people were on methadone (6%) as a form of MOUD, while most were on buprenorphine or buprenorphine/naloxone (94%). Nearly half (49%) of the cohort was on the HCV DAA medication, glecaprevir/pibrentasvir (Mavyret). At baseline, the study sample also had high prevalence of co-occurring psychiatric diagnoses (other substance use: 65%; anxiety: 41%, depression: 37%). Three percent of the cohort also had recorded history of an opioid overdose during the baseline period (n=84).

When these characteristics were stratified by year of cohort entry, there were characteristics that changed over time. The proportion of the cohort comprising Medicaid beneficiaries increased from 48% in 2015 to 88% by 2019, which is likely an artifact of the changing underlying population of Commercial beneficiaries included in MarketScan. The proportion of people with a co-occurring substance use also increased from 58% in 2015 to 70% in 2019. Alcohol, cannabis, cocaine, and other stimulant use diagnosis prevalences increased over time (Figure 2). Methadone use decreased from 14% in 2015 to 2% in 2019. The HCV DAA therapy mix at cohort entry also varied over time (Table 1 and Figure 1). Later cohort entrants were less likely to have chronic liver disease/cirrhosis (2015: 27%, 2019: 10%). All other included characteristics remained stable over time (Table 1).

Eleven percent of the overall cohort discontinued HCV DAA therapy prior to eight weeks (n=326). When stratified by year of cohort entry, early discontinuation was unstable over time (2015: 13%; 2016: 7%; 2017: 11%; 2018: 14%; 2019: 10%). Overall, younger adults (18-35), female, those with OUD and another SUD, those with an opioid overdose during the baseline

period, and people diagnosed anxiety or depression were more likely to discontinue DAA therapy prior to 8 weeks.

The results of the overall adjusted analysis and adjusted analysis stratified by insurance type are presented in Table 5. Younger age ($RD_{36\text{-}50 \text{ vs. } 18\text{-}35}$: -0.03; 95% CI: -0.03,-0.01; $RD_{51\text{-}64 \text{ vs. } 18\text{-}35}$: -0.04; 95% CI: -0.07,-0.01), female sex ($RD_{\text{female vs. male}}$: 0.02, 95% CI: 0,0.05), Medicaid insurance ($RD_{\text{Medicaid vs. Commercial}}$: 0.01, 95% CI: -0.02,0.03), depression (RD: 0.01, 95% CI: -0.01,0.04), and anxiety (RD: 0.02, 95% CI: 0,0.04) were associated with an increased risk of early HCV DAA discontinuation.

Among people with Medicaid insurance, adults ages 36-50 years old and adults ages 51-64 years old had 3 fewer early DAA discontinuations per 100 people in comparison to adults ages 18-35 years (RD36-50 vs. 18-35: -0.03; 95% CI: -0.06,0.01; RD51-64 vs. 18-35: -0.03; 95% CI: -0.06,0.01). Conversely, those with depression or anxiety had 1 more early DAA early discontinuations per 100 people in comparison to those without depression or anxiety ($RD_{\text{depression}}$: 0.01 95% CI: -0.02,0.04; RD_{anxiety}: 0.01, 95% CI: -0.01,0.04).

The type of DAA formulation was associated with a risk of early discontinuation in the overall study sample. Initiating sofosbuvir/Velpatasvir (Epclusa), in comparison to glecaprevir/pibrentasvir (Mavyret), was associated with one more early DAA discontinuations per 100 people (RD: 0.01; 95% CI: -0.03,0.05). Among Medicaid beneficiaries, differences in discontinuation by HCV DAA type persisted ($RD_{\text{Harvoni vs. Mavyret}}$: 0.03, 95% CI: -0.03,0.09; $RD_{\text{Epclusa vs. Mavyret}}$: 0.01, 95% CI: -0.03,0.05). When limiting the Medicaid sample to when

Mavyret was on the market (September 2017-December 2019), the relationship became even more stark ($RD_{\text{Harvoni vs. Mavyret}}$: 0.21; 95% CI: -0.01,0.44; $RD_{\text{Epclusa vs. Mavyret:}}$ 0.02; 95% CI: -0.04,0.08).

Among people with commercial insurance, the results remained similar except for the risk of discontinuation associated with different HCV DAA formulations. The risk of discontinuation was lower among older people in comparison to those ages 18-35 ($RD_{\text{36-50 vs. 18-35}}$: -0.07 , 95% CI: -0.12,-0.02; $RD_{\text{51-64 vs. 18-35}}$: -0.07, 95% CI: -0.11,-0.02), and the presence of non-OUD substance use was associated an two more discontinuations per 100 people (RD: 0.02; 95% CI: -0.02,0.07). In contrast to the overall and Medicaid only results, there was less evidence for differences in risk of early discontinuations between types of DAA treatments ($RD_{\text{Harvoni vs. Mavyret}}$: -0.04, 95% CI: -0.12,0.04; $RD_{\text{Epclusa vs. Mavyret}}$: 0.01, 95% CI: -0.08,0.09).

Discussion

In this retrospective cohort of over 2,000 insured adults on MOUD who initiated HCV DAA therapy between 2015 and 2019, we investigated patient characteristics and predictors of early DAA treatment discontinuation. Over time, the median age of cohort entrants decreased (2015: 49 (interquartile range (IQR): 30-57); 2019: 37 (IQR:31-46)), the prevalence of additional substance use diagnoses at baseline increased (2015: 58%; 2019: 70%), and the cohort transitioned from mostly initiating ledipasvir/sofosbuvir (proprietary name: Harvoni) in 2015 (59%) to mostly initiating glecaprevir/pibrentasvir (proprietary name: Mavyret) by 2019 (77%). Among the youngest cohort entrants (18-35 years old), 13% discontinued HCV DAA therapy early. Among the oldest cohort entrants (51-64), 9% discontinued early. Twelve percent of

people with an additional substance use diagnosis at baseline discontinued their HCV DAA therapy early. In contrast, 10% of people with OUD alone discontinued their HCV DAA therapy early. These proportions remained similar regardless of commercial or Medicaid insurance source.

This study observed a high prevalence of co-occurring psychiatric conditions among participants, which aligns with findings from previous research on HCV DAA treatment in populations with substance use disorders.[30,32,39–41] The high co-occurrence of mental health conditions with opioid use disorder presents a challenge for treatment. This co-occurrence can make it difficult for clinicians to effectively manage both conditions simultaneously.[39–41] However, it also creates an opportunity to improve patient care. Public health officials and clinicians can leverage this opportunity by ensuring access to quality psychiatric care specifically trained in treating both OUD and co-occurring mental health conditions. Additionally, healthcare providers should prioritize identifying and treating these additional conditions to optimize patient care.[39–41]

The present analysis revealed surprising variations in treatment adherence by HCV DAA type, with Commercial and Medicaid patients adhering differently to specific treatment options. Previous studies have shown regimen-specific characteristics such as pill burden and length of treatment to be predictors of HCV DAA adherence.[39,40,50] HCV DAA therapy in general has not been associated with significant adverse effects affecting adherence.[51] The one exception to this is sofosbuvir+ribavirin (Sovaldi) which has greater side effects and toxicities due to the inclusion of ribavirin.[52] Higher risk of early discontinuation among those on sofosbuvir+ribavirn from the current study support this. Beyond sofosbuvir+ribavirin (Sovaldi), varying associations between

treatment regimens by insurance type would suggest that these differences may reflect differences in underlying population characteristics not captured in other covariates than the medications themselves. In theory, HCV DAA choice would be based on HCV genotype, prior treatment, and liver damage.[53] However, due to payer rationing, insurance coverage is often the predominant deciding factor.[54] Different insurers and state Medicaid programs have varying preferred DAA formularies and varying pre-authorization requirements, which may impact which patients are prescribed which medications. It may also be possible that these associations are spurious and are due to random error due to the relatively small cell sizes in the nonadherence groups in the Medicaid and Commercial analyses. Further studies with larger numbers of patients on HCV DAA regimens other than sofosbuvir/velpatasvir (Epclusa) and ledipasvir/sofosbuvir (Harvoni) would provide better precision to investigate this potential relationship.

In the current study, younger age was associated with early HCV DAA discontinuation, which is consistent with previous research.[39,55,56] A possible explanation for this elevated early discontinuation risk is the presence of multiple substance use disorders. Younger age has been associated with a greater degree of polysubstance use.[57] Predictors of discontinuation in the overall study population were similar when analysis was limited to those 18-35 years old. Further research on the causes of early HCV DAA discontinuation among young people is especially important because people ages 20-39 had the highest acute HCV incidence in the US in 2021.[5]

Our study has multiple clinical implications. In our cohort, medication adherence was high (89%) overall, which is a proportion similar to studies examining patients without OUD.[55] Interestingly, the early discontinuation risk in this study was higher than or similar to other claims-based studies in populations with substance use disorders.[39–41] The level of adherence needed to obtain sustained virologic response (SVR) after 12+ weeks of treatment is unknown.[58] However, in a cohort study with SVR data and with medication adherence similar to the present study, SVR was achieved in 96% of cohort participants.[55] In our study, patients with additional SUD diagnoses had a marginally higher risk of medication nonadherence, which suggests that they may need additional supports.[59] HCV DAA therapy initiation may itself be a path into effective treatment for co-occurring SUD.[60] Combined OUD and HCV treatment in previous studies has shown higher MOUD adherence and less opioid and cocaine use in comparison to those with HCV on MOUD alone.[28,61]

There are two potential limitations of the present study. Prescription drug claims data may not have provided a complete picture of adherence to HCV DAA treatment. Most patients only need two to three refills of their initial prescription to complete the treatment. Simplifying adherence into two categories (less than 8 weeks and 8 weeks or more) may have missed important variation in how patients take their medication. Certain patient characteristics might appear insignificant or even reversed in their importance if we consider the full range of adherence patterns. In contrast, another potential concern, misclassification of the outcome due to cash payment, is unlikely to be a significant issue. Misclassification in this case would occur if people paying cash for medication are incorrectly classified as having poor adherence (less than 8 weeks) simply because of the payment method, not their actual behavior. However, the high cost

of HCV DAA therapy, often exceeding $1,000 per pill,[62] makes it highly improbable that patients with insurance would pay cash, reducing the chance of this type of information bias.

Conclusion

In this study sample of 2,935 insured individuals treated for OUD who initiated HCV DAA therapy between 2015 and 2019, patients had high levels of psychiatric comorbidities, co-occurring substance use, and chronic liver disease. Despite having high levels of potential risk factors for early discontinuation, the overall proportion of people who discontinued HCV DAA therapy prior to eight weeks was similar to that observed in populations without OUD. This suggests that OUD should not be used as exclusionary criteria for payer authorization of these life-saving medications.

Tables and Figures

Table 2-1: Baseline Characteristics of Cohort (N=2,935)

	Total N=2,935	2015 N=247	2016 N=419	2017 N=548	2018 N=862	2019 N=859
Demographics						
Age (Years), median (IQR)	38 (31-52)	49 (30-57)	45 (32-56)	39 (31-54)	37 (30-49)	37 (31-46)
Age Groups, n (%)						
18-35	1,210 (100%)	78 (6%)	140 (12%)	228 (19%)	391 (32%)	373 (31%)
36-50	919 (100%)	58 (6%)	111 (12%)	142 (15%)	283 (31%)	325 (35%)
51-64	806 (100%)	111 (14%)	168 (21%)	178 (22%)	188 (23%)	161 (20%)
Sex, n (%)						
Male	1,515 (100%)	159 (10%)	258 (17%)	305 (20%)	423 (28%)	370 (24%)
Female	1,420 (100%)	88 (6%)	161 (11%)	243 (17%)	439 (31%)	489 (34%)
Insurance Source, n (%)						
Commercial	826 (100%)	129 (16%)	221 (27%)	190 (23%)	183 (22%)	103 (12%)
Medicaid	2,109 (100%)	118 (6%)	198 (9%)	358 (17%)	679 (32%)	756 (36%)

Medications						
Discontinued HCV DAA prior to 8 weeks, n (%)	326 (11%)	32 (13%)	30 (7%)	61 (11%)	117 (14%)	86 (10%)
Type of MOUD, n (%)						
Methadone	162 (100%)	34 (21%)	54 (33%)	33 (20%)	20 (12%)	21 (13%)
Buprenorphine or Buprenorphine/Naloxone	2,773 (100%)	213 (8%)	365 (13%)	515 (19%)	842 (30%)	838 (30%)
HCV DAA Type, n (%)						
Epclusa	484 (100%)	0 (0%)	67 (14%)	158 (33%)	96 (20%)	163 (34%)
Harvoni or Harvoni/ Sovaldi	668 (100%)	146 (22%)	214 (32%)	194 (29%)	85 (13%)	29 (4%)
Mavyret	1,435 (100%)	0 (0%)	0 (0%)	102 (7%)	670 (47%)	663 (46%)
Sovaldi	68 (100%)	32 (47%)	36 (53%)	0 (0%)	0 (0%)	0 (0%)
Viekira Pak or Viekira Xr	93 (100%)	50 (54%)	39 (42%)	4 (4%)	0 (0%)	0 (0%)
Zepatier	120 (100%)	0 (0%)	20 (17%)	89 (74%)	10 (8%)	1 (1%)
Other	67 (100%)	19 (28%)	43 (64%)	1 (1%)	1 (1%)	3 (4%)
Clinical Characteristics						
Chronic Liver Disease/Cirrhosis, n (%)						
No	2,485 (100%)	180 (7%)	339 (14%)	457 (18%)	739 (30%)	770 (31%)
Yes	450 (100%)	67 (15%)	80 (18%)	91 (20%)	123 (27%)	89 (20%)
Depression, n (%)						
No	1,843 (100%)	165 (9%)	275 (15%)	359 (19%)	538 (29%)	506 (27%)
Yes	1,092 (100%)	82 (8%)	144 (13%)	189 (17%)	324 (30%)	353 (32%)
Anxiety Disorder, n (%)						
No	1,725 (100%)	159 (9%)	262 (15%)	320 (19%)	505 (29%)	479 (28%)
Yes	1,210 (100%)	88 (7%)	157 (13%)	228 (19%)	357 (30%)	380 (31%)
Opioid Overdose, n (%)						
No	2,851 (100%)	241 (8%)	409 (14%)	528 (19%)	840 (29%)	833 (29%)
Yes	84 (100%)	6 (7%)	10 (12%)	20 (24%)	22 (26%)	26 (31%)
Other Substance Use, n (%)						
No	1,019 (100%)	103 (10%)	197 (19%)	209 (21%)	256 (25%)	254 (25%)
Yes	1,916 (100%)	144 (8%)	222 (12%)	339 (18%)	606 (32%)	605 (32%)
Alcohol Use, n (%)						
No	2,453 (100%)	221 (9%)	355 (14%)	451 (18%)	713 (29%)	713 (29%)
Yes	482 (100%)	26 (5%)	64 (13%)	97 (20%)	149 (31%)	146 (30%)
Cannabis Use, n (%)						

No	2,539 (100%)	225 (9%)	378 (15%)	479 (19%)	738 (29%)	719 (28%)
Yes	396 (100%)	22 (6%)	41 (10%)	69 (17%)	124 (31%)	140 (35%)
Cocaine Use, n (%)						
No	2,601 (100%)	231 (9%)	390 (15%)	479 (18%)	754 (29%)	747 (29%)
Yes	334 (100%)	16 (5%)	29 (9%)	69 (21%)	108 (32%)	112 (34%)
Other Psychoactive or Stimulant Use, n (%)						
No	2,065 (100%)	198 (10%)	339 (16%)	401 (19%)	564 (27%)	563 (27%)
Yes	870 (100%)	49 (6%)	80 (9%)	147 (17%)	298 (34%)	296 (34%)

Table 2-2: Baseline Characteristics of Cohort by HCV DAA Early Discontinuation Status (N=2,935)

	Total N=2,935	No Discontinuation N=2,609	Discontinued Prior to 8 Weeks N=326
Demographics			
Age (years), median (IQR)	38 (31-52)	39 (31-52)	36 (28-49)
Age Groups, n (%)			
18-35	1,210 (100%)	1,050 (87%)	160 (13%)
36-50	919 (100%)	828 (90%)	91 (10%)
51-64	806 (100%)	731 (91%)	75 (9%)
Sex, n (%)			
Male	1,515 (100%)	1,364 (90%)	151 (10%)
Female	1,420 (100%)	1,245 (88%)	175 (12%)
Insurance Source, n (%)			
Commercial	826 (100%)	743 (90%)	83 (10%)
Medicaid	2,109 (100%)	1,866 (88%)	243 (12%)
Index Date (Year), n (%)			
2015	247 (100%)	215 (87%)	32 (13%)
2016	419 (100%)	389 (93%)	30 (7%)
2017	548 (100%)	487 (89%)	61 (11%)
2018	862 (100%)	745 (86%)	117 (14%)
2019	859 (100%)	773 (90%)	86 (10%)
Medications			
Type of MOUD, n (%)			
Methadone	162 (100%)	147 (91%)	15 (9%)

Buprenorphine or Buprenorphine/Naloxone	2,773 (100%)	2,462 (89%)	311 (11%)
HCV DAA Type, n (%)			
Epclusa	484 (100%)	424 (88%)	60 (12%)
Harvoni or Harvoni/Sovaldi	668 (100%)	610 (91%)	58 (9%)
Mavyret	1,435 (100%)	1,274 (89%)	161 (11%)
Sovaldi	68 (100%)	55 (81%)	13 (19%)
Viekira Pak or Viekira Xr	93 (100%)	77 (83%)	16 (17%)
Zepatier	120 (100%)	106 (88%)	14 (12%)
Other	67 (100%)	-	-
Clinical Characteristics			
Chronic Liver Disease/Cirrhosis, n (%)			
No	2,485 (100%)	2,207 (89%)	278 (11%)
Yes	450 (100%)	402 (89%)	48 (11%)
Depression, n (%)			
No	1,843 (100%)	1,651 (90%)	192 (10%)
Yes	1,092 (100%)	958 (88%)	134 (12%)
Anxiety Disorder, n (%)			
No	1,725 (100%)	1,551 (90%)	174 (10%)
Yes	1,210 (100%)	1,058 (87%)	152 (13%)
Opioid Overdose, n (%)			
No	2,851 (100%)	2,541 (89%)	310 (11%)
Yes	84 (100%)	68 (81%)	16 (19%)
Other Substance Use, n (%)			
No	1,019 (100%)	917 (90%)	102 (10%)
Yes	1,916 (100%)	1,692 (88%)	224 (12%)
Alcohol Use, n (%)			
No	2,453 (100%)	2,178 (89%)	275 (11%)
Yes	482 (100%)	431 (89%)	51 (11%)
Cannabis Use, n (%)			
No	2,539 (100%)	2,272 (89%)	267 (11%)
Yes	396 (100%)	337 (85%)	59 (15%)
Cocaine Use, n (%)			
No	2,601 (100%)	2,316 (89%)	285 (11%)
Yes	334 (100%)	293 (88%)	41 (12%)
Other Psychoactive or Stimulant Use, n (%)			
No	2,065 (100%)	1,843 (89%)	222 (11%)
Yes	870 (100%)	766 (88%)	104 (12%)

Table 2-3: Baseline Characteristics of Analytic Cohort by HCV DAA Early Discontinuation Status, Medicaid Only (N=2,109)

	Total	No Discontinuation	Discontinued Prior to 8 weeks
	N=2,109	N=1,866	N=243
Demographics			
Age (Years), median (IQR)	40 (33-52)	40 (33-52)	38 (31-50)
Age Groups, n (%)			
18-35	773 (100%)	671 (87%)	102 (13%)
36-50	759 (100%)	678 (89%)	81 (11%)
51-64	577 (100%)	517 (90%)	60 (10%)
Sex, n (%)			
Male	956 (100%)	856 (90%)	100 (10%)
Female	1,153 (100%)	1,010 (88%)	143 (12%)
Index Date (Year), n (%)			
2015	118 (100%)	98 (83%)	20 (17%)
2016	198 (100%)	187 (94%)	11 (6%)
2017	358 (100%)	313 (87%)	45 (13%)
2018	679 (100%)	588 (87%)	91 (13%)
2019	756 (100%)	680 (90%)	76 (10%)
Medications			
Type of MOUD, n (%)			
Methadone	113 (100%)	102 (90%)	11 (10%)
Buprenorphine or Buprenorphine/Naloxone	1,996 (100%)	1,764 (88%)	232 (12%)
HCV DAA Type, n (%)			
Epclusa	269 (100%)	237 (88%)	32 (12%)
Harvoni or Harvoni/Sovaldi	242 (100%)	216 (89%)	26 (11%)
Mavyret	1,365 (100%)	1,212 (89%)	153 (11%)
Sovaldi	31 (100%)	-	-
Viekira Pak or Viekira Xr	58 (100%)	47 (81%)	11 (19%)
Zepatier	113 (100%)	99 (88%)	14 (12%)
Other	31 (100%)	-	-
Clinical Characteristics			
Chronic Liver Disease/Cirrhosis, n (%)			

No	1,781 (100%)	1,577 (89%)	204 (11%)
Yes	328 (100%)	289 (88%)	39 (12%)
Depression, n (%)			
No	1,275 (100%)	1,134 (89%)	141 (11%)
Yes	834 (100%)	732 (88%)	102 (12%)
Anxiety Disorder, n (%)			
No	1,186 (100%)	1,058 (89%)	128 (11%)
Yes	923 (100%)	808 (88%)	115 (12%)
Opioid Overdose, n (%)			
No	2,061 (100%)	1,830 (89%)	231 (11%)
Yes	48 (100%)	36 (75%)	12 (25%)
Other Substance Use, n (%)			
No	620 (100%)	549 (89%)	71 (11%)
Yes	1,489 (100%)	1,317 (88%)	172 (12%)
Alcohol Use, n (%)			
No	1,776 (100%)	1,572 (89%)	204 (11%)
Yes	333 (100%)	294 (88%)	39 (12%)
Cannabis Use, n (%)			
No	1,832 (100%)	1,627 (89%)	205 (11%)
Yes	277 (100%)	239 (86%)	38 (14%)
Cocaine Use, n (%)			
No	1,868 (100%)	1,654 (89%)	214 (11%)
Yes	241 (100%)	212 (88%)	29 (12%)
Other Psychoactive or Stimulant Use, n (%)			
No	1,460 (100%)	1,289 (88%)	171 (12%)
Yes	649 (100%)	577 (89%)	72 (11%)

Table 2-4: Baseline Characteristics of Analytic Cohort by HCV DAA Early Discontinuation Status, Commercial Only (N=826)

	Total	No Discontinuation	Discontinued Prior to 8 Weeks

	N=826	N=743	N=83
Demographics			
Age (Years), median (IQR)	34 (25-54)	35 (25-54)	26 (24-41)
Age Groups, n (%)			
18-35	437 (100%)	379 (87%)	58 (13%)
36-50	160 (100%)	150 (94%)	10 (6%)
51-64	229 (100%)	214 (93%)	15 (7%)
Sex, n (%)			
Male	559 (100%)	508 (91%)	51 (9%)
Female	267 (100%)	235 (88%)	32 (12%)
Index Date (Year), n (%)			
2015	129 (100%)	117 (91%)	12 (9%)
2016	221 (100%)	202 (91%)	19 (9%)
2017	190 (100%)	174 (92%)	16 (8%)
2018	183 (100%)	157 (86%)	26 (14%)
2019	103 (100%)	93 (90%)	10 (10%)
Medications			
Type of MOUD, n (%)			
Methadone	49 (100%)	-	-
Buprenorphine or Buprenorphine/Naloxone	777 (100%)	698 (90%)	79 (10%)
HCV DAA Type, n (%)			
Epclusa	215 (100%)	187 (87%)	28 (13%)
Harvoni or Harvoni/Sovaldi	426 (100%)	394 (92%)	32 (8%)
Mavyret	70	-	-
Sovaldi	37	-	-
Viekira Pak or Viekira Xr	35	-	-
Other	43	-	-
Clinical Characteristics			
Chronic Liver Disease/Cirrhosis, n (%)			
No	704 (100%)	630 (89%)	74 (11%)

Yes	122 (100%)	113 (93%)	9 (7%)
Depression, n (%)			
No	568 (100%)	517 (91%)	51 (9%)
Yes	258 (100%)	226 (88%)	32 (12%)
Anxiety Disorder, n (%)			
No	539 (100%)	493 (91%)	46 (9%)
Yes	287 (100%)	250 (87%)	37 (13%)
Opioid Overdose, n (%)			
No	790 (100%)	711 (90%)	79 (10%)
Yes	36 (100%)	-	-
Other Substance Use, n (%)			
No	399 (100%)	368 (92%)	31 (8%)
Yes	427 (100%)	375 (88%)	52 (12%)
Alcohol Use, n (%)			
No	677 (100%)	606 (90%)	71 (10%)
Yes	149 (100%)	137 (92%)	12 (8%)
Cannabis Use, n (%)			
No	707 (100%)	645 (91%)	62 (9%)
Yes	119 (100%)	98 (82%)	21 (18%)
Cocaine Use, n (%)			
No	733 (100%)	662 (90%)	71 (10%)
Yes	93 (100%)	81 (87%)	12 (13%)
Other Psychoactive or Stimulant Use, n (%)			
No	605 (100%)	554 (92%)	51 (8%)
Yes	221 (100%)	189 (86%)	32 (14%)

Table 2-5: Adjusted marginal risk differences comparing risk of early discontinuation (<8 weeks of HCV DAA Supply) between levels of baseline variables of interest.

	Commercial & Medicaid	Medicaid Only	Commercial Only	Medicaid Post-Mavyret Approval**
Demographics				
Age, years (categorical)				
36-50 vs 18-35	-0.03 [-0.06,-0.01]	-0.03 [-0.06,0.01]	-0.07 [-0.12,-0.02]	-0.02 [-0.06,0.01]
51-64 vs 18-35	-0.04 [-0.07,-0.01]	-0.03 [-0.06,0.01]	-0.07 [-0.11,-0.02]	-0.01 [-0.05,0.04]
Female (vs. Male)	0.02 [0,0.05]	0.02 [-0.01,0.05]	0.03 [-0.02,0.07]	0.02 [-0.01,0.06]
Medicaid Insurance (vs. Commercial)[b]	0.01 [-0.02,0.03]		-	-
Psychiatric Diagnoses				
Other Substance Use (vs. OUD only)	0.01 [-0.02,0.03][a]	0 [-0.03,0.03][e]	0.02 [-0.02,0.07][e]	0 [-0.04,0.03][e]
Depression[b]	0.01 [-0.01,0.04]	0.01 [-0.02,0.04]	0.02 [-0.02,0.07]	0.01 [-0.02,0.04]
Anxiety[b]	0.02 [0,0.04]	0.01 [-0.01,0.04]	0.03 [-0.01,0.07]	0.02 [-0.01,0.05]
Medications				
Hepatitis C Direct Acting Antiviral Type				
Harvoni vs. Mavyret	0 [-0.04,0.05][*,c]	0.03 [-0.03,0.09][∀,b]	-0.04 [-0.12,0.04][#,b]	0.21 [-0.01,0.44][∞,b]
Epclusa vs. Mavyret	0.01 [-0.03,0.05][*,c]	0.01 [-0.03,0.05][∀,b]	0.01 [-0.08,0.09][#,b]	0.02 [-0.04,0.08][∞,b]
Buprenorphine (vs. Methadone)	-0.07 [-0.18,0.04][d]	-0.06 [-0.18,0.06][b]	-0.07 [-0.32,0.19][b]	-0.08 [-0.31,0.14][b]
Observations	2,935	2,109	826	1,597

95% confidence intervals in brackets; OUD= Opioid use disorder; *: Sample Size = 2,587; ∀:Sample Size=1,876; #:Sample Size=711; ∞: Sample Size= 1,556; **= Sept 1, 2017-Dec 31, 2019; a= Adjusted for age, sex, anxiety, depression, Medicaid vs. Commercial insurance; b=Adjusted for age and sex; c=Adjusted for age, sex, cirrhosis, Medicaid vs. Commercial insurance; d=Adjusted for age, sex, Medicaid vs. Commercial insurance; e=Adjusted for age, sex, anxiety, depression

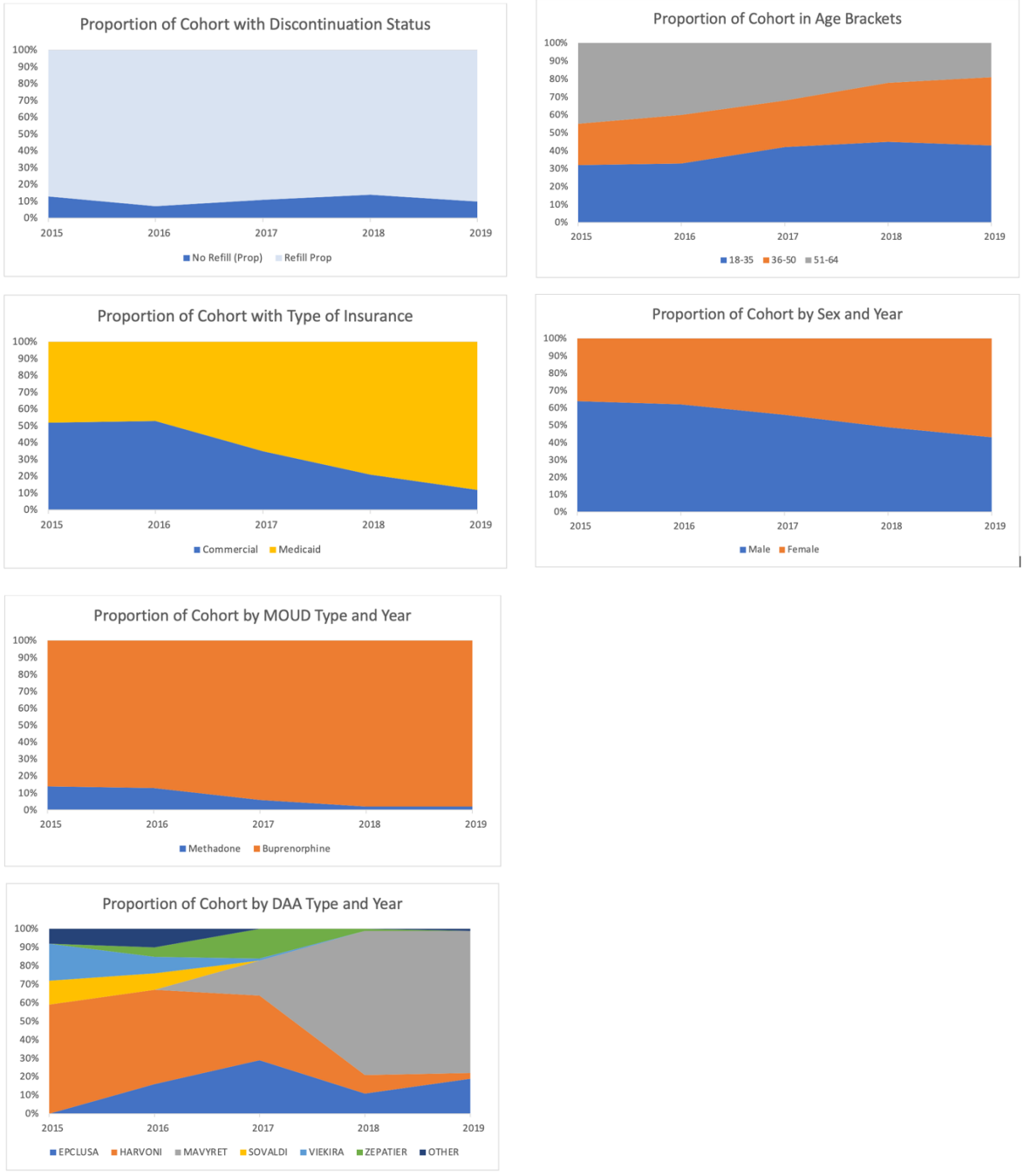


Figure 2-1: Proportion Plots of Baseline Characteristics Across Cohort Entry Years

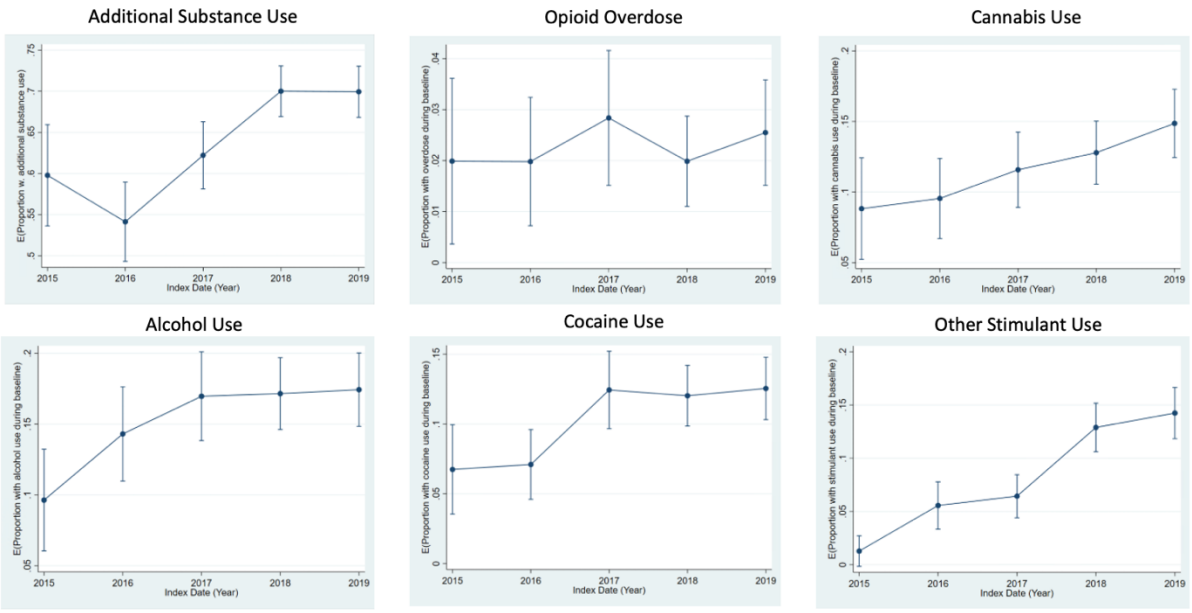


Figure 2-2: Age and Sex-Adjusted Baseline Substance Use Diagnosis Prevalence, by Year of Cohort Entry

Appendix

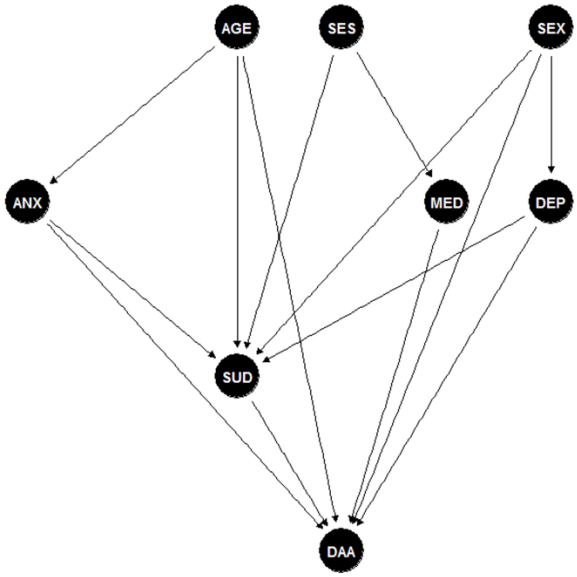
Supplementary Table 2-1: Baseline Characteristics of Cohort by discontinuation status (N=1,210), ages 18-35 years only

	Total	No Discontinuation	Discontinued Prior to 8 Weeks
	N=1,210	N=1,050	N=160
Age (Years), median (IQR)	29 (25-32)	29 (25-33)	28 (25-32)
Sex, n (%)			
Male	515 (100%)	456 (89%)	59 (11%)
Female	695 (100%)	594 (85%)	101 (15%)
Insurance Type, n (%)			
Commercial	437 (100%)	379 (87%)	58 (13%)
Medicaid	773 (100%)	671 (87%)	102 (13%)
Type of MOUD, n (%)			
Methadone	14 (100%)	-	-
Buprenorphine or Buprenorphine/Naloxone	1,196 (100%)	1,040 (87%)	156 (13%)
HCV DAA Type, n (%)			

Epclusa	236 (100%)	198 (84%)	38 (16%)
Harvoni or Harvoni/Sovaldi	258 (100%)	231 (90%)	27 (10%)
Mavyret	612 (100%)	535 (87%)	77 (13%)
Other	24 (100%)	-	-
Sovaldi	27 (100%)	-	-
Viekira Pak or Viekira Xr	28 (100%)	-	-
Zepatier	25 (100%)	-	-
Chronic Liver Disease/Cirrhosis, n (%)			
No	1,103 (100%)	957 (87%)	146 (13%)
Yes	107 (100%)	93 (87%)	14 (13%)
Depression, n (%)			
No	746 (100%)	653 (88%)	93 (12%)
Yes	464 (100%)	397 (86%)	67 (14%)
Anxiety Disorder, n (%)			
No	686 (100%)	601 (88%)	85 (12%)
Yes	524 (100%)	449 (86%)	75 (14%)
Opioid Overdose, n (%)			
No	1,156 (100%)	1,007 (87%)	149 (13%)
Yes	54 (100%)	43 (80%)	11 (20%)
Other Substance Use, n (%)			
No	371 (100%)	330 (89%)	41 (11%)
Yes	839 (100%)	720 (86%)	119 (14%)
Alcohol Use, n (%)			
No	1,004 (100%)	871 (87%)	133 (13%)
Yes	206 (100%)	179 (87%)	27 (13%)
Cannabis Use, n (%)			
No	981 (100%)	854 (87%)	127 (13%)
Yes	229 (100%)	196 (86%)	33 (14%)
Cocaine Use, n (%)			
No	1,037 (100%)	899 (87%)	138 (13%)
Yes	173 (100%)	151 (87%)	22 (13%)
Other Psychoactive or Stimulant Use, n (%)			
No	761 (100%)	665 (87%)	96 (13%)
Yes	449 (100%)	385 (86%)	64 (14%)

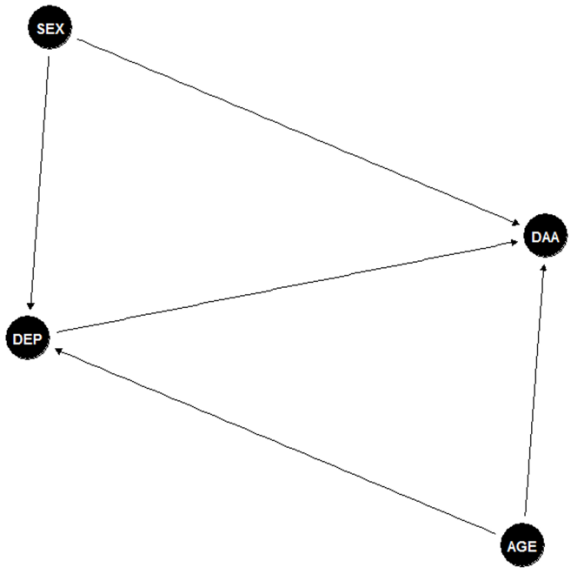
Supplemental Figures

Directed Acyclic Graphs (DAGs)



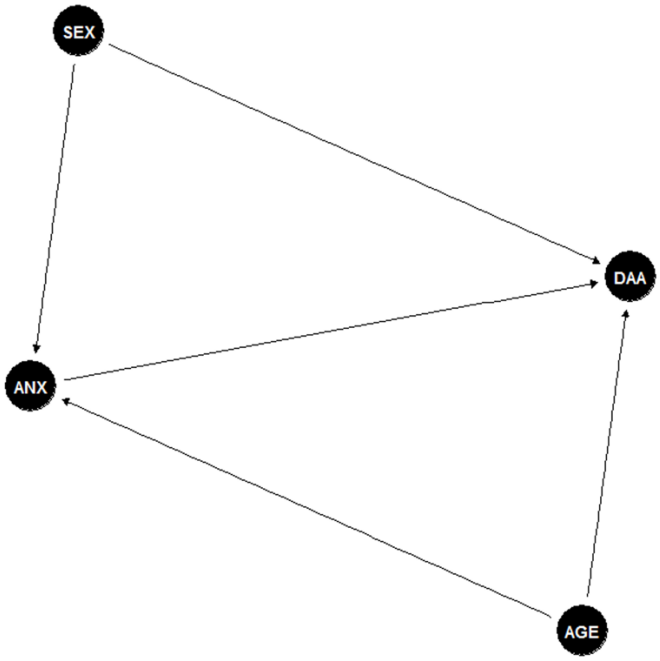
Supplementary Figure 2-1: Directed acyclic graph (DAG) depicting relationships between baseline diagnosis for additional substance use (SUD) and early discontinuation of Hepatitis C direct acting antiviral treatment (DAA) during follow-up.

Covariates collected at baseline (180 days prior to Hepatitis C DAA initiation): anxiety (ANX), depression (DEP), age (AGE), sex (SEX), Medicaid vs. Commercial Insurance (MED); Unobserved covariates: socioeconomic status (SES).



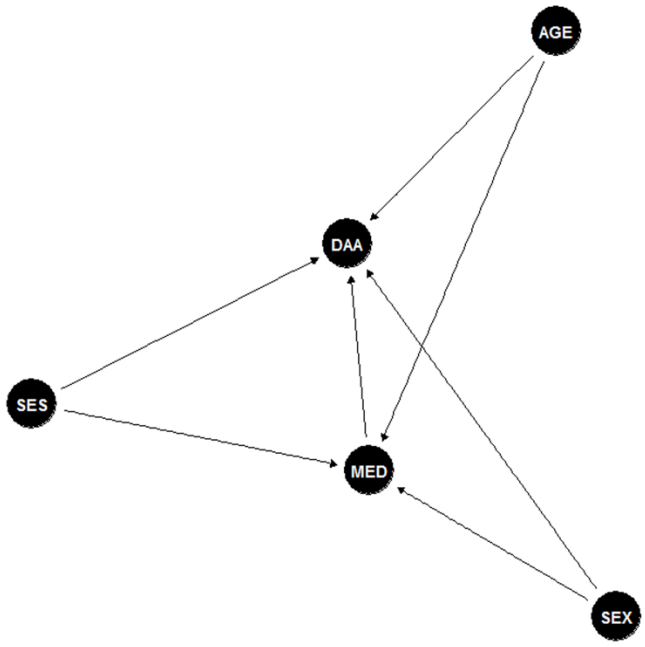
Supplementary Figure 2-2: Directed acyclic graph (DAG) depicting relationships between baseline diagnosis for depression (DEP) and early discontinuation of Hepatitis C direct acting antiviral treatment (DAA) during follow-up.

Covariates collected at baseline 180 days prior to Hepatitis C DAA initiation): age (AGE), sex (SEX).



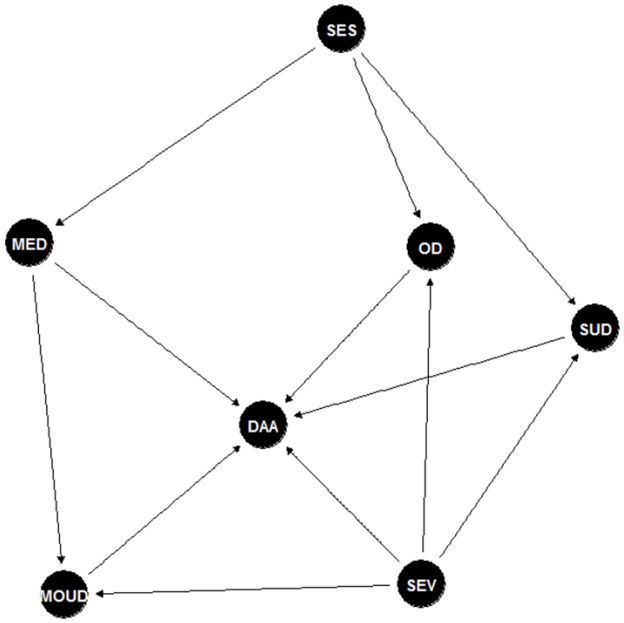
Supplementary Figure 2-3: Directed acyclic graph (DAG) depicting relationships between baseline diagnosis for anxiety (ANX) and early discontinuation of Hepatitis C direct acting antiviral treatment (DAA) during follow-up.

Covariates collected at baseline (180 days prior to Hepatitis C DAA initiation): age (AGE), sex (SEX).



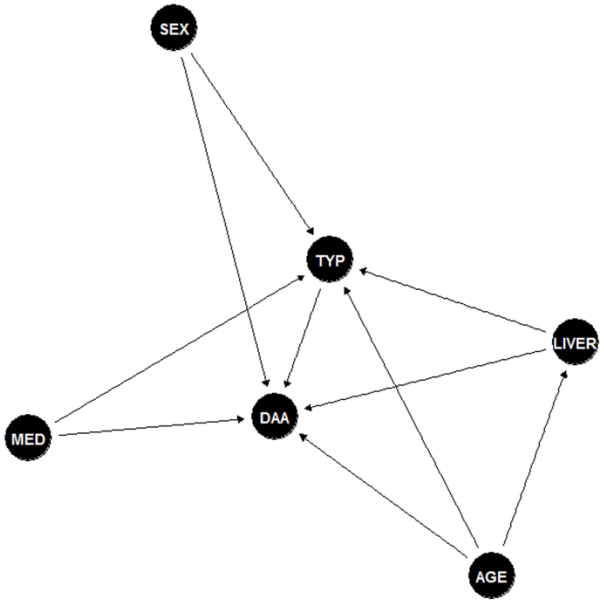
Supplementary Figure 2-4: Directed acyclic graph (DAG) depicting relationships between type of insurance (Medicaid vs. Commercial, MED) and early discontinuation of Hepatitis C direct acting antiviral treatment (DAA) during follow-up.

Covariates collected at baseline (180 days prior to Hepatitis C DAA initiation): age (AGE), sex (SEX); Unobserved covariates: socioeconomic status (SES).



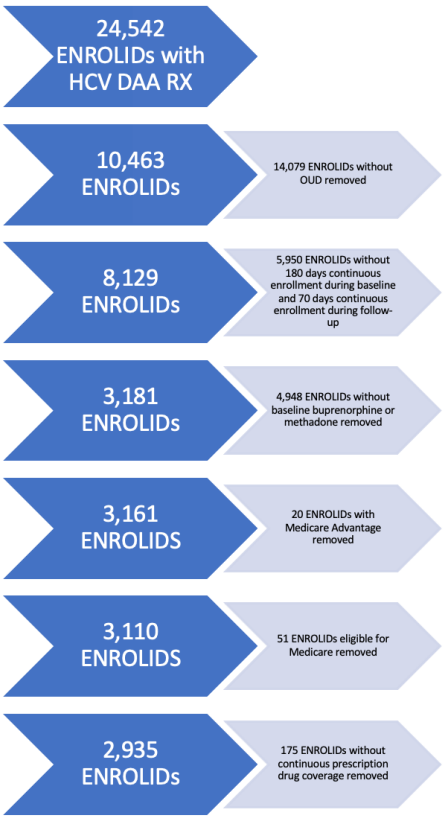
Supplementary Figure 2-5: Directed acyclic graph (DAG) depicting relationships between type of opioid agonist therapy used during baseline (MOUD) and early discontinuation of Hepatitis C direct acting antiviral treatment (DAA) during follow-up.

Covariates collected at baseline (MOUD) and early discontinuation of Hepatitis C direct acting antiviral treatment (DAA) during follow-up. Covariates collected at baseline (180 days prior to Hepatitis C DAA initiation): age (AGE), sex (SEX), overdose (OD), additional substance use (SUD), Medicaid vs. Commercial Insurance (MED); Unobserved covariates: socioeconomic status (SES), opioid use disorder severity (SEV).

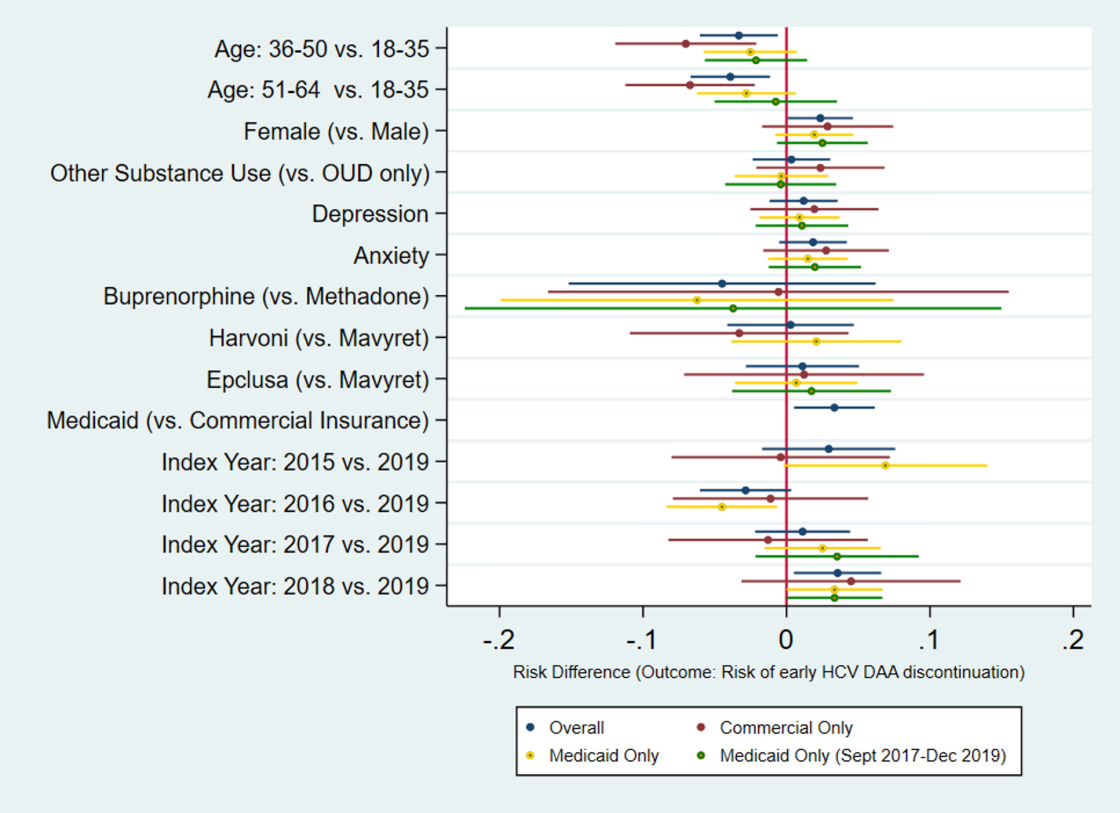


Supplementary Figure 2-6: Directed acyclic graph (DAG) depicting relationships between type of Hepatitis C direct acting antiviral initiated at cohort entry (TYP) and early discontinuation of Hepatitis C direct acting antiviral treatment (DAA) during follow-up.

Covariates collected at baseline (180 days prior to Hepatitis C DAA initiation): age (AGE), sex (SEX), Medicaid vs. Commercial Insurance (MED), cirrhosis (LIVER).



Supplementary Figure 2-7: Study flow diagram depicting how cohort was constructed.



Age, Sex, Year are crude; Other substance use adjusted for age (linear), female, anxiety, depression, Medicaid status; Depression and anxiety are adjusted for age (3rd degree polynomial), sex, and Medicaid status; Buprenorphine vs Methadone is adjusted for: age (linear), sex, and Medicaid status; Hepatitis C Direct Acting Antiviral Type is adjusted for: age (3rd degree polynomial), sex, liver disease or cirrhosis status at baseline, and Medicaid status; Medicaid is adjusted for: age (3rd degree polynomial) and sex

Supplementary Figure 2-8: Results of inverse-probability of treatment weighting analyses

Chapter 3 Effect of ART regimen type on buprenorphine adherence among privately and publicly insured people living with HIV and using buprenorphine for the treatment of opioid use disorder, 2015-2019 (Aim 2)

Introduction

Opioid use disorder (OUD) is a complex condition characterized by compulsive use of opioid drugs, regardless of a person's wishes to stop use or the adverse effects of opioid use on the person's physical or emotional well-being.[1,63] OUD is increasingly common in the United States.[2] In 2020, 2.7 million people aged twelve years and older had OUD in the United States.[2] Between 2020 and 2021, nearly 150,000 people have died due to an overdose involving opioids in the US.[63]

Medication for opioid use disorder is the gold-standard treatment for OUD.[64] In particular, buprenorphine, a partial opioid agonist and form of opioid agonist therapy, is associated with significantly less hospital use and fewer overdose events, particularly when taken for one year or more.[10] However, treatment persistence is a challenge for many patients. In an IQVIA administrative claims dataset containing over one million buprenorphine treatment episodes from 2009 through 2018, 70% of people on buprenorphine treatment stopped before six months.[65] Buprenorphine or naltrexone forms of medication for OUD (vs. methadone), male sex, younger age, baseline psychiatric diagnoses, benzodiazepine use, stimulant use, and lack of behavioral health therapy during treatment have all been associated with decreased medication for OUD persistence.[66] Addressing treatment adherence and persistence is essential because short-term treatment is unlikely to provide lasting patient benefits.[67] Moreover, immediately after treatment cessation, overdose mortality risk starkly increases.[68]

OUD is prevalent among people living with HIV and is a crucial driver of new HIV cases in the US.[69] The gold standard treatment for HIV is antiretroviral therapy (ART),[70] which includes protease inhibitors (PIs). PI use can result in drug interactions with buprenorphine and lead to higher-than-expected levels in the body.[71–74] Competitive binding to the same hepatic enzyme and enzyme inhibition by ART PIs can lead to slower metabolism of buprenorphine, which leads to higher blood concentrations. High buprenorphine plasma concentrations may lead to lower required doses to maintain buprenorphine treatment and persistence in people on PIs versus other types of ART therapy.

Studies examining biological interaction between opioid agonist therapy medications and HIV ART therapy in real-world cohorts are minimal. Co-administration of some forms of ART and buprenorphine changes buprenorphine and buprenorphine metabolite serum concentrations in pharmacokinetic studies.[71–77] However, these studies had small sample sizes (<45 participants total) of people who did not have HIV and were not taking other ART medications. This is often the case in pharmacokinetic studies because of the difficulty in enrolling people living with HIV and OUD who are not taking interacting concomitant medications and are healthy enough to participate in these time-intensive studies.[73] Understanding real-world patterns of concomitant buprenorphine and ART use can inform whether the changes in buprenorphine or buprenorphine metabolite serum concentrations observed in pharmacokinetic studies extend to settings where patients are using other commonly interacting therapies. Pharmacokinetic studies have shown contrasting results to human liver cells in in vitro studies[75,76] emphasizing the importance of analyzing this research question in real world data.

The objective of this study was to examine whether co-use of ART PIs with buprenorphine leads to better buprenorphine treatment adherence among patients living with HIV and OUD using a large administrative database. Additionally, we aimed to examine whether co-use of ART PIs with buprenorphine lead to equivalent buprenorphine treatment adherence at low doses of buprenorphine than would be required in the absence of PIs.

Methods

Data and Study Design

The MarketScan Commercial and Multi-State Medicaid databases contain information on individual-level paid claims that is longitudinal and linkable between service types and across different health providers and health plans. Claims in the commercial database are populated from commercial insurance companies with broad geographic coverage. The Multi-State Medicaid data includes data from seven million Medicaid recipients in eleven state Medicaid programs and Medicaid Managed Care programs.

We constructed a retrospective cohort of people with OUD who filled prescriptions for ART and buprenorphine or buprenorphine/naloxone between January 1, 2015, and December 31, 2019. OUD was defined using inpatient and outpatient services and outpatient pharmacy dispensing records.[44] We used outpatient pharmacy dispensing records to identify prescription fills for buprenorphine and ARTs based on their generic names. We excluded buprenorphine formulations not indicated for the treatment of OUD, such as Belbuca and Butrans. People on emtricitabine/tenofovir without an accompanying HIV diagnosis in the baseline period were excluded because this medication is prescribed for pre-exposure prophylaxis and not for HIV

treatment. Patients were required to have at least one day of overlap between the expected use periods of their ART and buprenorphine prescriptions, and the index date was defined as the first day of expected overlap. We excluded people who had fewer than 90 days of continuous enrollment with prescription drug coverage before and less than 180 days after the index date to ensure possibility of capturing a full treatment episode (Figure 1). Hepatitis B diagnosis is a contraindication for many protease inhibitors, thus, those with an HBV diagnosis in the baseline period were excluded. Patients were allowed to have started ART or buprenorphine first, which means that both incident and prevalent prescriptions of ART and buprenorphine were included.

Exposure

Exposure was grouped into two categories: exposure to an ART PI vs exposure to a non-PI ART. People who filled a prescription for atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir were considered exposed to PI. People who filled a prescription for ART not containing these medications were considered unexposed. Exposure was determined in the fourteen days after the index date regardless of later switches to other ART medication types. Fourteen days were allotted to allow for patients to pick up all ART prescriptions that were part of their ART therapy.

Buprenorphine Proportion of Days Covered (PDC)

Buprenorphine medication adherence was defined based on the proportion of days covered (PDC)[78,79] during follow-up (Figure 1). People with at least 80% of the 180 days of follow-up covered by a buprenorphine prescription were considered adherent.[80] If people had overlapping buprenorphine prescriptions, the overlapping days' supply was added to the end of the buprenorphine continuous use period.[81]

Buprenorphine Persistence

Buprenorphine persistence was defined as the number of days between the index date and the discontinuation date of their first buprenorphine continuous use period. Discontinuation was defined as a period of 14 days without a buprenorphine prescription after the expected end of supply from the previous buprenorphine prescription.

Covariates

Demographic and clinical characteristics were collected during the 90-day baseline period before the index date. Age and sex were collected from the index claim. Information on baseline mental health diagnoses such as depression, bipolar disorder, anxiety, schizophrenia, and other co-occurring substance use disorders (alcohol, cannabis, cocaine, hallucinogens, inhalants, and other stimulants or psychoactive substances) were collected from primary and secondary diagnoses on inpatient and outpatient claims. The occurrence of diagnosed opioid-related overdoses during the baseline period was also collected from primary and secondary diagnoses on inpatient and outpatient claims. Information on previous mental health diagnoses and other conditions required to calculate the Charlson Comorbidity Index were obtained from inpatient admission and outpatient services claims during the baseline period. The Charlson Comorbidity Index scores were computed using the 'charlson' user-generated module within Stata. The Appendix includes the ICD9/10 diagnosis codes for all covariate definitions.

Outpatient pharmacy dispensing claims during the baseline (90-day) period prior to index date were used to identify fills of medications that may be associated with buprenorphine adherence.[82–86] These medications include benzodiazepines[82–86] and prescription opioid analgesics not for the treatment of OUD.[85,86] Because patients were allowed to start either

buprenorphine or ART first, a variable was created to capture which medication was first initiated.

Differing Effects of PIs by Initial Buprenorphine Dose

We examined whether the effect of PIs on buprenorphine adherence and persistence differed by initial buprenorphine dose. Current approved prescribing information for Suboxone, a brand name buprenorphine/naloxone formulation, advises different induction schedules based on whether patients are dependent on short-acting or long-acting opioids. The label also suggests a target daily dose of 16mg/day for maintenance treatment.[87] However, in practice, induction schedules often vary by provider, setting, and country.[88] Patient-specific characteristics that may be associated with initial buprenorphine dose are injection drug use, race, gender, psychiatric symptoms and chronic pain.[88] Low buprenorphine daily dosage was defined as filling an initial prescription for buprenorphine of <16mg/day at the time of the index date. The cutoff (16mg buprenorphine/day) was chosen because previous studies have shown that buprenorphine daily doses of less than 16mg are suboptimal for abstinence syndrome prevention and long-term treatment adherence.[85] People on <16mg/day would be expected at baseline to have worse buprenorphine adherence over the following 180 days. However, because of suspected interactions with PIs, those exposed to a PI may have higher serum levels of buprenorphine and norbuprenorphine, leading to better adherence. Initial buprenorphine dose was corrected for probable measurement error in the quantity variable using median imputation. A detailed description of the imputation approach is provided in the appendix.

Statistical Analyses

Baseline characteristics were summarized as median and interquartile range (IQR) for continuous measures and frequency (%) for categorical measures by protease inhibitor exposure

status. [45] Continuous proportion of days covered by PI exposure was reported as median (IQR) and people with 80% proportion of days covered by PI exposure status were reported as frequencies and percent. Continuous buprenorphine persistence in days was reported as median (IQR) by PI exposure. In tabular analyses, we estimated crude odds ratios (ORs) of buprenorphine adherence comparing those exposed and unexposed to PIs, which we further stratified by initial buprenorphine dose. Cell sizes in the tabular analysis were inspected to ensure sizes of >5 people.

In adjusted models, confounders and variables strongly correlated only with the outcome were included as covariates. Confounders were selected based on a priori knowledge (age, sex, cocaine use) and numerical assessment of whether the variable was considerably correlated with both exposure and outcome independent of other included covariates (directed acyclic graph (DAG) presented in Figure S1). We estimated the adjusted association between PI exposure and buprenorphine adherence by initial buprenorphine dose (high vs. low) using logistic regression models. This model adjusted for sex, age, cocaine use diagnosis, Charlson Comorbidity Index score, Medicaid insurance plan type (vs. commercial), and whether buprenorphine or ART was initiated first. The adjusted $RERI_{OR}$, a measure of interaction on the additive scale, was then computed again from the adjusted estimates. [89,90] For the buprenorphine persistence outcome, Cox proportional hazards models were used to calculate the crude and adjusted hazard ratios comparing the hazard of buprenorphine discontinuation in the 180-day follow-up period between those exposed to a PI and those unexposed to a PI, controlling for sex, age, baseline benzodiazepine prescription, baseline cocaine use disorder diagnosis, baseline alcohol use disorder, Charlson Comorbidity Index score, and whether buprenorphine or ART was initiated first. Proportional hazards assumptions were assessed by examining correlation between the

Schoenfeld residuals of each included variable with time and the significance of predictors when included as time varying covariates.[91] Breslow-Day method was used to account for tied events. In the adjusted analyses to assess whether the effect of PIs on adherence and persistence varied by initial buprenorphine dose, we estimated associations within strata of initial buprenorphine dose and in comparison to the doubly-unexposed group (non-PI exposed with <16mg/day buprenorphine) as has been previously recommended.[92] Multiplicativity was assessed via a ratio of the within-strata effect estimates and the p-value on the interaction term from the logistic regression model and additivity was assessed using the $RERI_{OR}$.[92]

This study was reviewed by the University of California, Los Angeles (UCLA) Institutional Review Board and deemed not human subjects research. All analyses were completed in SAS 9.4 and Stata 16.1.

Results

There were 255 eligible people in the final analytical sample (208 non-PI exposed, 47 PI exposed). Baseline characteristics of the study sample and summaries of the outcome measures by exposure status are presented in Table 1. The sample was 36% female and 64% male, with a median age of 37 (IQR: 30-49). Most people had Medicaid insurance (76%). Nearly one-third had co-occurring mental health disorders (depression: 32%; anxiety: 29%) and 62% had co-occurring substance use. This sample also had high levels of co-occurring benzodiazepine (22%) and non-MOUD opioid analgesic prescriptions (24%). Buprenorphine/naloxone was the most common buprenorphine formulation (89%). About half (54%) of the study sample had initial buprenorphine doses of at least 16mg/day, and it was slightly more common to initiate ART before buprenorphine (59%).

Baseline demographics, insurance type (Medicaid vs. commercial) and overall baseline health status as measured by the Charlson Comorbidity Index did not vary by type of PI. However, baseline mental health diagnoses varied slightly by PI exposure. The prevalence of bipolar disorder (BPD) and a cocaine use disorder were higher among patients exposed to PI's than non-PI's at baseline. Both non-PI exposed and PI-exposed groups were more likely to initiate ART before buprenorphine. However, among those on a PI medication, the prevalence of ART initiation before buprenorphine was much higher than that of the non-PI exposed (72% vs 56%).

The median proportion of days covered (PDC) was the same for both groups (median PDC_{non-PI}=1 [IQR: 0.47-1.00]; median PDC_{PI}=1 [IQR: 0.47-1.00]). Fifty-two percent of patients on a non-PI were adherent to their buprenorphine (PDC≥80%) and 51% of patients on a PI were adherent to their buprenorphine. The crude odds ratio comparing the odds of being adherent among those on a PI vs. those on a non-PI was 0.95 (95% CI: 0.48,1.88). After stratifying by initial buprenorphine dose, the ORs among those on low and high doses of buprenorphine were similar. The odds of being adherent among those exposed to ART PIs was 0.96 (95% CI: 0.35, 2.59) times that of those on a non-PI among those on a low buprenorphine dose, and the odds of adherence among those on PIs were 1.08 (95% CI: 0.39, 3.24) times that of those on a non-PI among those on a high buprenorphine dose. The results of a Mantel-Haenszel test supported the conclusion of no difference between the two stratified OR estimates (Mantel Haenszel p=0.86).

The results of the adjusted proportion of days covered analysis are presented in Table 2. After adjusting for sex, age, cocaine use diagnosis, Charlson Comorbidity Index, and Medicaid insurance plan type (vs. Commercial), and whether buprenorphine or ART was initiated first, the

results from the crude analysis changed slightly. The odds of ≥80% proportion of days covered among those exposed to PIs was 1.02 (95% CI: 0.38, 2.75) times that of those exposed to a non-PI among those on a low buprenorphine dose. The odds of ≥80% proportion of days covered among those exposed to ART PIs was 1.53 (95% CI: 0.53,4.43) times that of those exposed to a non-PI form of ART among those on a high buprenorphine dose. The adjusted analyses show a divergence between the stratum-specific ORs, but the estimates are imprecise. The $RERI_{OR}$ was 1.14 (95% CI: -2.36,4.64) and the ratio of the ORs was 1.50 (0.36, 6.32). The $RERI_{OR}$ suggested possible superadditive effects and the ratio of the ORs suggests possible supermultiplicative effects. Again though, these estimates were imprecise. The results of the proportion of days covered analyses did not meaningfully change when the proportion of days covered in the 180-day follow-up period was varied between 0.50 and 1.00 (Figure 3).

Buprenorphine treatment persistence differed by type of ART (median $duration_{non\text{-}PI}$=115 days [IQR: 35-302]; median $duration_{PI}$=74 [IQR: 30-281]), but these estimates were also imprecise and did not meet statistical significance (Wilcoxon rank-sum test p-value: 0.40). The crude hazard ratio (HR) comparing the hazard of discontinuation among those exposed to PIs vs. those unexposed to PIs was 1.12 (95% CI: 0.74,1.67). A Kaplan Meier curve stratified by type of ART is presented in Figure 2. After stratifying by initial buprenorphine dose, the hazard ratios in both initial buprenorphine doses were similar. The hazard of discontinuation among those exposed to ART PIs was 1.13 (95% CI: 0.67,1.91) times that of those exposed to a non-PI form of ART among those on a low buprenorphine dose. The hazard of discontinuation among those exposed to ART PIs was 1.01 (95% CI: 0.36,1.65) times that of those exposed to a non-PI form of ART

among those on a high buprenorphine dose. The results of test for proportional hazards were insignificant (p= 0.51).

The results of the adjusted buprenorphine persistence analysis are presented in Table 3. We adjusted for sex, age, cocaine use diagnosis, Charlson Comorbidity Index score, insurance type, and whether buprenorphine or ART was initiated first. Among those on a high initial dose of buprenorphine, the hazard of discontinuation for those on a PI form of ART was very similar to those on a non-PI form of ART ($HR_{PI\ vs.\ non\text{-}PI}$: 0.99 [95% CI: 0.35, 1.64]). Among those on a low initial dose of buprenorphine the results were little changed ($HR_{PI\ vs.\ non\text{-}PI}$: 1.06 [95% CI: 0.63, 1.81]). The $RERI_{OR}$ was -0.07 (95% CI: -0.80, 0.67) and the ratio of the HRs was 0.94 (95% CI: 0.14,1.73), again suggesting little evidence for effect modification of the HR on both the additive and multiplicative scales, respectively. The results of test for proportional hazards were again insignificant (p= 0.92), suggesting that the proportional hazards assumption was met.

Discussion

In the study of 255 people living with and receiving pharmacotherapy for HIV and OUD, there were small to no marked differences in buprenorphine adherence and persistence across protease inhibitor vs. a non-protease inhibitor forms of ART. Estimates for the effect of protease inhibitors on buprenorphine adherence (proportion of days covered) over the 180-day period following the beginning of co-use of ART and buprenorphine were different between those on low and high initial doses of buprenorphine. Among those on a low initial dose of buprenorphine (<16mg/day), protease inhibitor exposure had little effect on adherence. However, among those on a high or minimally adequate initial dose of buprenorphine (≥16mg/day), adherence appeared to increase possibly. However, likely due to the small sample size, these estimates were

imprecise. In contrast, the results of the persistence analysis did not support an effect of protease inhibitor exposure on time to buprenorphine discontinuation in the 180-day period following the beginning of co-use of ART and buprenorphine. Reviewed in their entirety, these analyses provide weak to no evidence for the effect of PI exposure on buprenorphine adherence and persistence.

The present study results using real-world data are consistent with previous pharmacokinetic and pharmacodynamic studies of the interaction between ART protease inhibitors and buprenorphine.[72–74] Though buprenorphine utilizes an enzyme in the human liver that is inhibited by ART protease inhibitors, this does not appear to translate into a strong clinically significant effect of PI ART on buprenorphine adherence or persistence at the population level. This study adds to evidence that buprenorphine and PI co-prescription likely will not lead to harmful impacts on buprenorphine adherence. Additionally, previous research has also shown that buprenorphine, combined with highly active antiretroviral therapy (HAART), a form of ART of which PIs are a component, has little consequence for ART effectiveness.[93]

Heterogeneity of the effects of PIs on opioid agonist therapy occurs across specific types of PIs and across people.[75] Different PIs have varying abilities to interact with buprenorphine.[75] Their differing abilities to decrease the metabolism of buprenorphine is mainly due to their differing affinities for the CYP450 3A4 enzyme.[75] One in vivo study even reported an increase in methadone metabolism and accompanying opioid withdrawal symptoms in the presence of lopinavir,[76,77] though this result has been inconsistent and potentially opioid agonist therapy dose-dependent.[77] Due to present small sample size, we were unable to stratify the results of this

study by type of PI. Collapsing all PIs into a single category may have drowned the effects of potent PI-induced enzyme inhibition among PIs with weaker enzyme inhibition potential. Both in vitro and in vivo studies have also found large inter-individual variation in the effect of PIs on opioid agonist therapy metabolism.[75,76] Large inter-individual variation and PI effect variation may have reduced our ability to discern a precise effect of PIs on buprenorphine adherence.

HIV ART treatment regimen decisions (e.g. PI- vs non-PI- based) are often based on clinical and demographic characteristics of patients as well as the healthcare providers' prescribing preferences.[94] In this study sample, women, people with diagnosed bipolar disorder, depression, or cocaine abuse, dependence, or poisoning were more likely to be on PI ARTs than non-PI ART regimens. These associations are consistent with previous literature.[94,95] Women of childbearing age are preferentially prescribed PI-based regimens due to the potential teratogenicity of NNRTIs.[94,95] Teratogenicity has not been supported in human studies but has been observed in non-human primates.[96] Patients with a perceived higher risk of ART discontinuation at baseline such as PWID, people using cocaine, or those with neuropsychiatric conditions, are often placed on PI-based regimens due to the lower risk of viral resistance in comparison to other forms of ART.[93–95,97–102] Lack of ART adherence can lead to drug resistance in people living with HIV.[103] Some NNRTIs have also been linked with central nervous system and psychological adverse events, and in some cases these adverse events led to ART treatment discontinuation.[104] Because of this, patients with neuropsychiatric conditions at baseline are more likely to receive PIs.[94,95]

Injection drug use, cocaine use, depression, and other neuropsychiatric disorders are associated with decreased adherence on opioid agonist therapy.[105–108] Our ability to control for confounding

through these factors was dependent on their diagnosis and capture in administrative claims data. For example, baseline depression status and other neuropsychiatric conditions are readily identifiable via ICD diagnosis codes, which is a valid identification method,[109] while injection drug use and cocaine use are harder to classify. Injection drug use does not have a specific ICD code, though injection drug use may be deduced through algorithmic methods with highly varying sensitivity and specificity.[110] Cocaine use would be captured if a person was diagnosed with cocaine abuse, dependence, or poisoning during a healthcare visit or hospital admission.[111] Residual confounding, which in this case would likely negatively bias our estimates, may be present if these factors associated with PI receipt and opioid agonist therapy adherence are not sufficiently controlled for. Future quantitative bias analysis can illuminate the level of misclassification needed on factors such as injection drug use, cocaine use, and psychiatric disorders to change confounding control meaningfully and thus the results of the present study.

Information on HIV subtypes is not available in claims data. Some subtypes of HIV-1 have shown primary resistance against PIs or NNRTIs, impacting the type of ART an individual receives. Age and sex are potentially associated with acquiring a non-subtype-B HIV infection[112] and with adherence to buprenorphine.[85] Because we were able to control for age and sex, confounding due to this association is unlikely to affect our estimates.

We did not have information on any medications and services people received that were not paid for through insurance. Self-pay is a significant form of payment for buprenorphine, but payment through insurance is still most common.[113] Even though self-pay status may be linked to buprenorphine adherence, self-pay status is unlikely to cause bias given that it is improbable that

self-pay status would cause which type of ART (PI vs. non-PI) a patient receives. This limits the generalizability of these study results to only those people who use commercial or Medicaid insurance to obtain buprenorphine and ART treatment but is unlikely to affect internal validity of the study.

Opioid agonist therapy can interact with other medications to clinically significant levels leading to serious adverse drug interactions. Co-use of benzodiazepines with methadone or buprenorphine can increase the risk of accidental injury or overdose.[84,114–116] In contrast, administering rifampin for tuberculosis treatment in conjunction with methadone can precipitate serious opioid withdrawal symptoms sometimes requiring the doubling of recommended methadone doses.[117] As a result, close monitoring of drug interactions among patients treated for comorbid conditions is warranted.

The high prevalence of co-occurring diagnosed depression and anxiety as well as benzodiazepine co-use was interesting. One third of the present cohort had a depression or anxiety diagnosis during the baseline period (90-days pre-cohort entry) and approximately 20% had an outpatient prescription fill for a benzodiazepine. This high prevalence of comorbid psychiatric diagnoses and benzodiazepine prescriptions is consistent with previous studies of people living with HIV with or without OUD and with OUD alone.[118–124] Studies that obtained depression and anxiety diagnosis from baseline questionnaires generally report higher prevalence of the two conditions.[118,120,121,124] This suggests that using depression and anxiety diagnosis on outpatient and inpatient encounter claims in the present study likely underestimated the true prevalence of clinically relevant anxiety and depression. Regardless, the anxiety, depression, and

benzodiazepine prevalence in our cohort is elevated above the national average among US adults (depression: 18.4%[125]; anxiety: 19.1%[126]; benzodiazepine use: 12.6%[127]). Depression, anxiety, and benzodiazepine use influence HIV and OUD treatment type[104], adherence [102,128], and overdose risk[84,114–116]. This highlights the complexity of treatment within the present study population and the potential for modifying effects of these three variables that may be the subject of further research.

Additionally, this study's findings prompt further research on non-ART PIs' effects on buprenorphine adherence. Protease inhibitors are components of medications to treat infections such as Hepatitis C and COVID-19. Both Hepatitis C and COVID-19 readily occur among people living with opioid use disorder,[129–131] highlighting the need for further research.

Among people on buprenorphine living with HIV, regardless of injection drug use, buprenorphine has been associated with increased ART uptake,[20] increased ART adherence,[21] and increased HIV viral suppression.[20] Whether buprenorphine treatment leads to improved HIV ART initiation rates and adherence or whether improved ART initiation or adherence leads to buprenorphine treatment uptake and adherence is poorly understood. Among PWID with HIV in Vancouver, Canada, opioid agonist therapy treatment impacted HIV treatment, but that there was not convincing evidence vice versa.[132] This underscores the importance of effective opioid agonist therapy treatment among people living with HIV. This study adds to this body of evidence that effective medication treatment of HIV and OUD will not likely be hampered or harmed by medication interactions between PIs and buprenorphine.

Conclusions

In this study using real-world data, there were no marked differences in buprenorphine adherence after exposure to an overlapping ART protease inhibitor vs. a non-protease inhibitor form of ART. To provide more precise estimates of the effect of PIs on buprenorphine adherence, future studies can employ data with more people taking HIV ART PIs.

Tables and Figures

Table 3-1: Baseline Demographic and Clinical Characteristics of Cohort (N=255)

	Total N=255	Non-Protease Inhibitor ART N=208	Protease Inhibitor ART N=47
Outcomes			
Proportion of days covered (continuous)	1 (0.46-1.00)	1 (0.47-1.00)	1 (0.47-1.00)
Proportion of days covered (binary, ≥80% = 1)	133 (52%)	109 (52%)	24 (51%)
Persistence±, days (continuous)	107 (35-292)	115 (35-302)	74 (30-281)
Demographic Information			
Age at Index Date (years)	37 (30-49)	37 (30-48)	43 (31-51)
Female	93 (36%)	71 (34%)	22 (47%)
Plan Type			
Commercial	62 (24%)	52 (25%)	10 (21%)
Medicaid	193 (76%)	156 (75%)	37 (79%)
Index Date (Year)			
2015	53 (21%)	40 (19%)	13 (28%)
2016	52 (20%)	44 (21%)	8 (17%)
2017	49 (19%)	35 (17%)	14 (30%)
2018	62 (24%)	53 (25%)	9 (19%)
2019	39 (15%)	36 (17%)	3 (6%)
Mental Health Diagnoses			
Depression	81 (32%)	64 (31%)	17 (36%)
Bipolar Disorder	39 (15%)	27 (13%)	12 (26%)
Anxiety	73 (29%)	61 (29%)	12 (26%)
Schizophrenia	14 (5%)	10 (5%)	4 (9%)
Opioid Overdose	13 (5%)	10 (5%)	3 (6%)
Other Substance Use	158 (62%)	123 (59%)	35 (74%)

Alcohol Use	25 (10%)	18 (9%)	7 (15%)
Cannabis Use	26 (10%)	22 (11%)	4 (9%)
Cocaine Use	37 (15%)	28 (13%)	9 (19%)
Other	66 (26%)	56 (27%)	10 (21%)
Other Medications			
Non-MOUD Opiate Rx	60 (24%)	43 (21%)	17 (36%)
Benzodiazepine Rx	55 (22%)	46 (22%)	9 (19%)
Bipolar Disorder Rx	21 (8%)	19 (9%)	2 (4%)
Overall Health Indexes			
Charlson Comorbidity Index	6 (0-7)	6 (0-7)	6 (1-7)
Initial Buprenorphine Prescription Information			
Buprenorphine Formulation			
Buprenorphine Hydrochloride	28 (11%)	23 (11%)	5 (11%)
Buprenorphine/Naloxone	227 (89%)	185 (89%)	42 (89%)
≥16 mg/day buprenorphine initial dose	159 (62%)	125 (60%)	34 (72%)
≥16 mg/day buprenorphine initial dose (corrected)	137 (54%)	115 (55%)	22 (47%)
Order of ART and Buprenorphine			
Buprenorphine initiated before ART	105 (41%)	92 (44%)	13 (28%)
ART initiated before buprenorphine	150 (59%)	116 (56%)	34 (72%)
Type of ART regimen			
Nucleoside/nucleotide reverse transcriptase Inhibitors (NRTI)	23 (9%)	23 (11%)	-
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	83 (33%)	83 (40%)	-
Integrase strand transfer inhibitor (INSTI)	72 (28%)	72 (35%)	-
NNRTI & INSTI	30 (12%)	30 (14%)	-
Protease Inhibitor (PI)	47 (18%)	-	47 (100%)
Protease Inhibitor Type			
Darunavir/Cobicistat			12 (20%)
Darunavir			15 (25%)
Ritonavir			23 (38%)
Other			11 (18%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures. IQR= interquartile range; ±= (date of first buprenorphine discontinuation during follow-up period)- (index date); Rx=Prescription; MOUD= Medication for Opioid User Disorder; ART= Antiretroviral therapy; "-" = data repressed due to small cell size; *= mental health removed from index values

Table 3-2: Modification of the effect of Initial Buprenorphine Dose and PI exposure on Buprenorphine Proportion of Days Covered (≥80%, vs <80%)

	Non-Protease Inhibitor (Non-PI)		Protease Inhibitor (PI)		
	N with/without PDC≥80%	OR* [95% CI]	N with/without PDC≥80%	OR* [95% CI]	ORs* [95% CI] for PI use within strata of initial buprenorphine dose
<16 mg/day buprenorphine	38/55	1 [Reference]	10/15	1.02 [0.38, 2.75]	1.02 [0.38, 2.75]
≥16 mg/day buprenorphine	71/44	2.19 [1.17, 4.09]	14/8	3.34 [1.13, 9.88]	1.53 [0.53, 4.43]

Measure of effect modification on additive scale: $RERI_{OR}$ [95% CI] = 1.14 [-2.36, 4.64]
Measures of effect modification on multiplicative scale: ratio of ORs [95% CI] = 1.50 [0.36, 6.32]; p-value for the interaction term between protease inhibitor exposure and buprenorphine dosage = 0.52
ORs are adjusted for sex, age, cocaine use diagnosis, Charlson Comorbidity Index, and Medicaid insurance plan type (vs. Commercial), and whether buprenorphine or ART was initiated first.

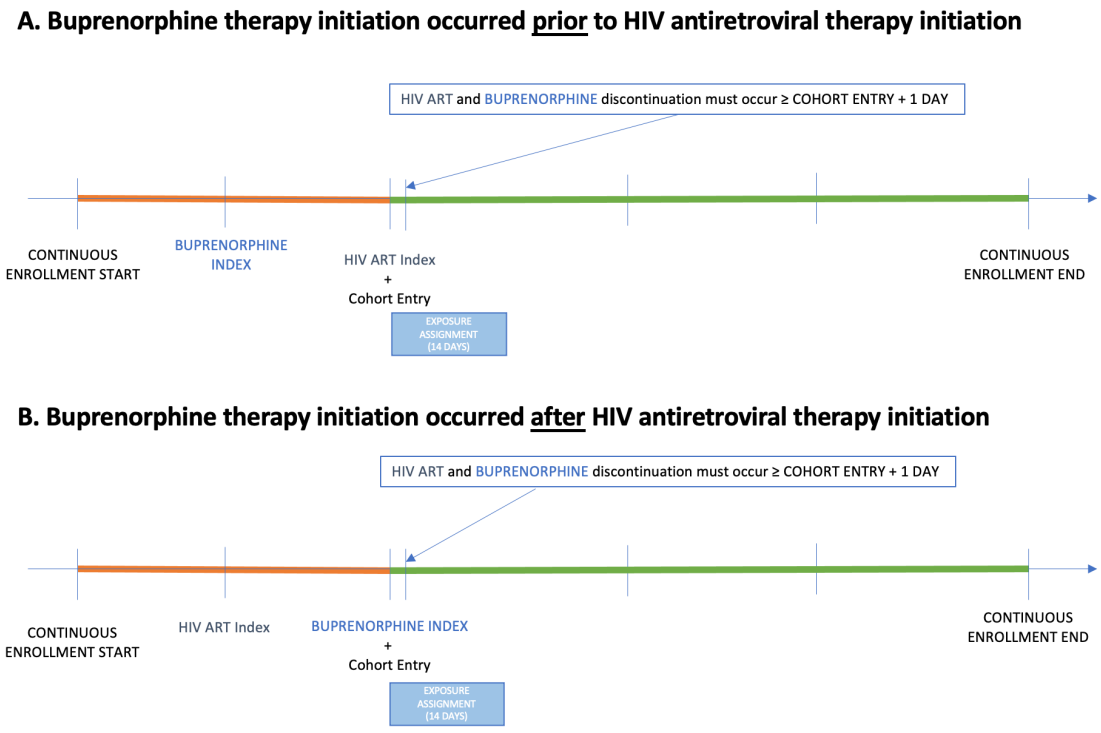
Table 3-3: Modification of the effect of Initial Buprenorphine Dose and PI exposure on Buprenorphine Persistence

	Non-Protease Inhibitor (non-PI)	Protease Inhibitor (PI)	
	HR* [95% CI]	HR* [95% CI]	HRs* [95% CI] for PI use within strata of initial buprenorphine dose
<16 mg/day buprenorphine	1 [Reference]	1.06 [0.63, 1.81]	1.06 [0.63, 1.81]
≥16 mg/day buprenorphine	0.71 [0.49,1.04]	0.71 [0.25, 1.17]	0.99 [0.35, 1.64]

Measure of effect modification on additive scale: $RERI_{OR}$ [95% CI] = -0.07 [-0.80, 0.67]

Measure of effect modification on multiplicative scale: ratio of HRs [95% CI] = 0.94 [0.14,1.73]; p-value for the interaction term between protease inhibitor exposure and buprenorphine dosage = 0.88
*HRs are adjusted for sex, age, baseline benzodiazepine prescription, baseline cocaine use diagnosis, baseline alcohol use, Charlson Comorbidity Index, and whether buprenorphine or ART was initiated first.
Persistence= time to buprenorphine discontinuation from Index Date; HR = hazard ratio; CI = confidence interval. Notes: The proportional hazards assumption was assessed by examining the correlation between the Schoenfeld residuals of each included variable with time, which tested for independence between these residuals and time.

Figure 3-1: Study Timeline and Proportion of Days Covered Calculation



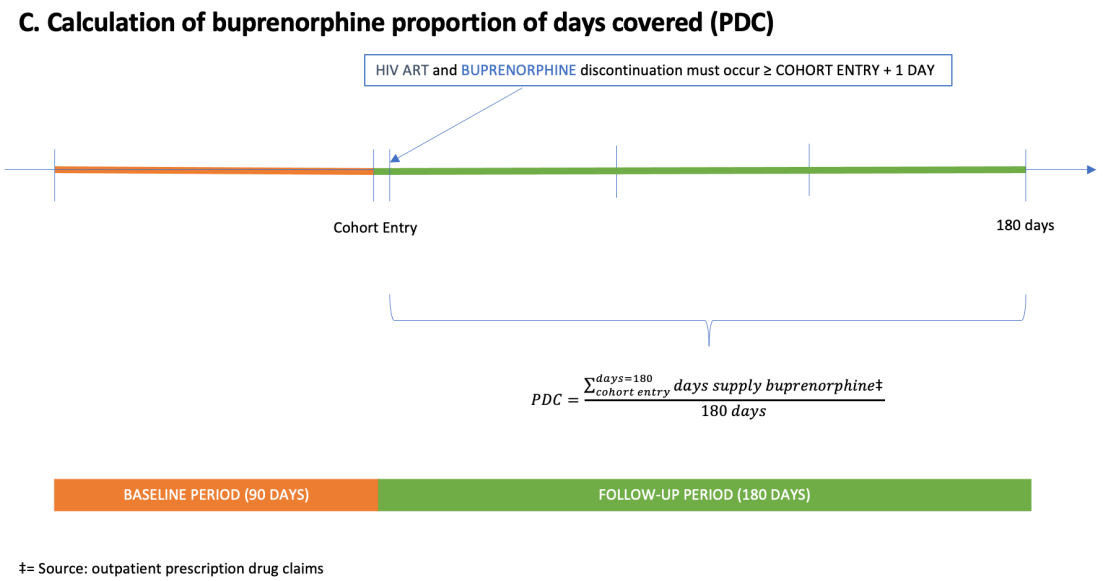
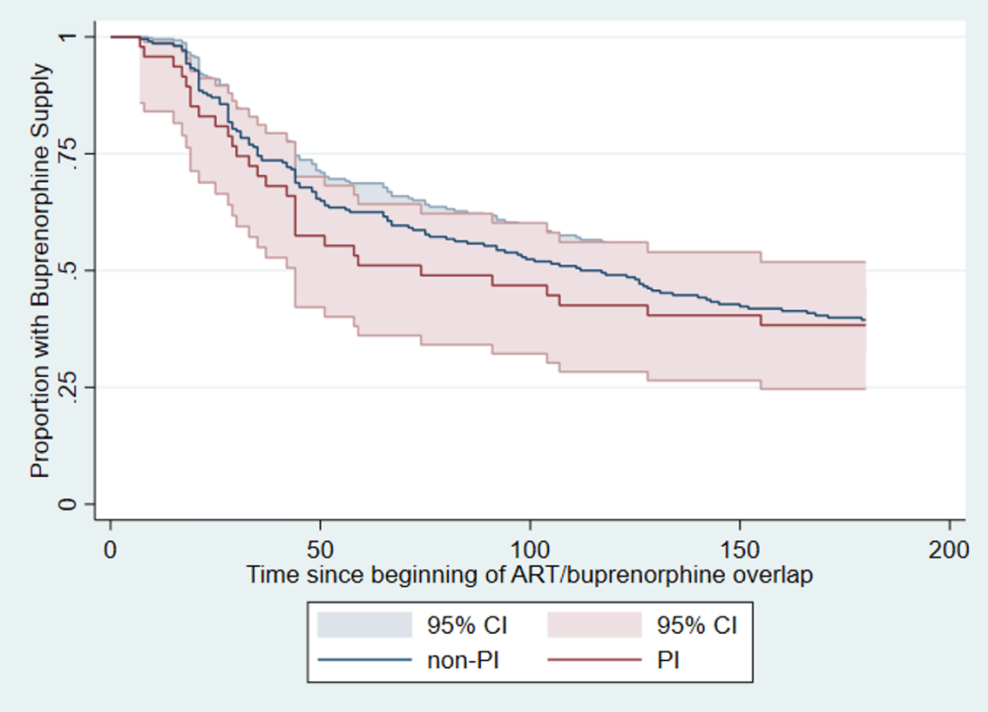
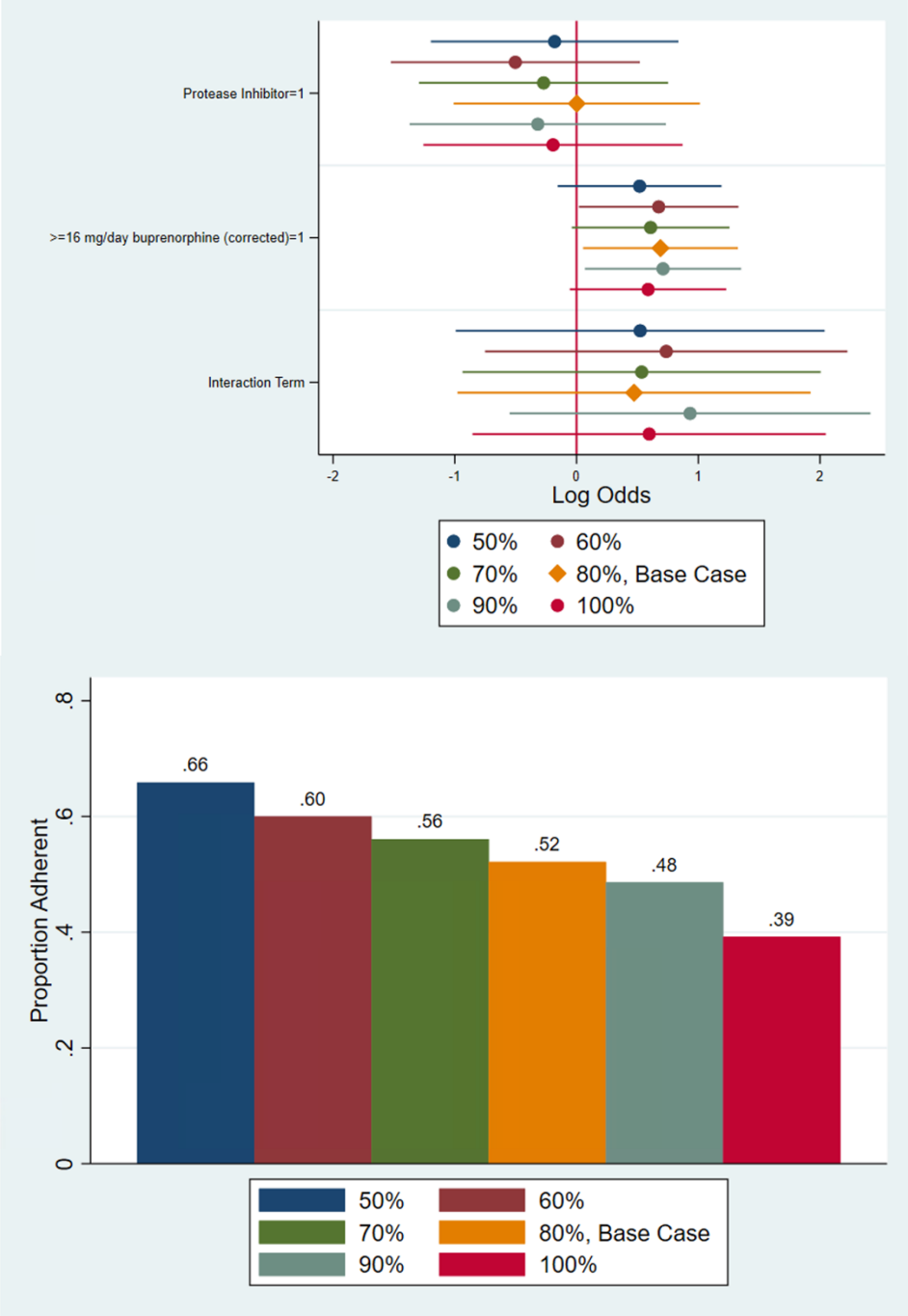


Figure 3-2: Kaplan Meier Survival Estimates for Buprenorphine Persistence, by Protease Inhibitor (PI) Exposure



CI= confidence interval

Figure 3-3: Sensitivity analyses varying the proportion of days covered (PDC) cutoff



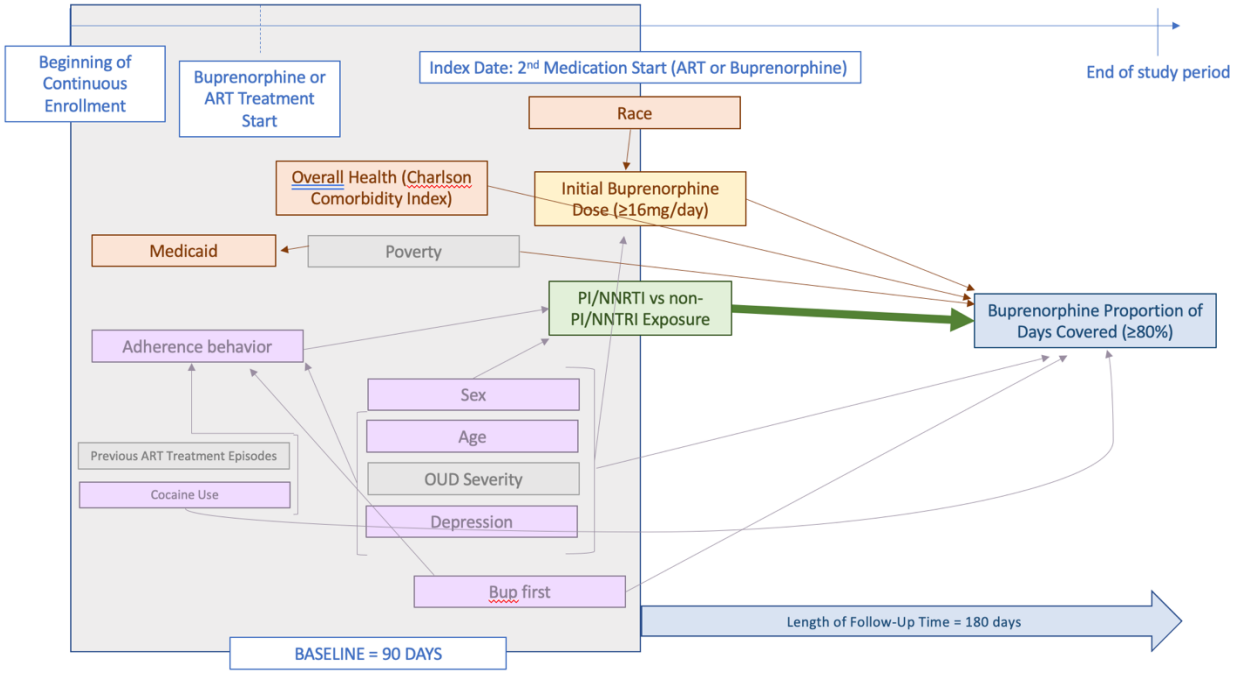
Appendix

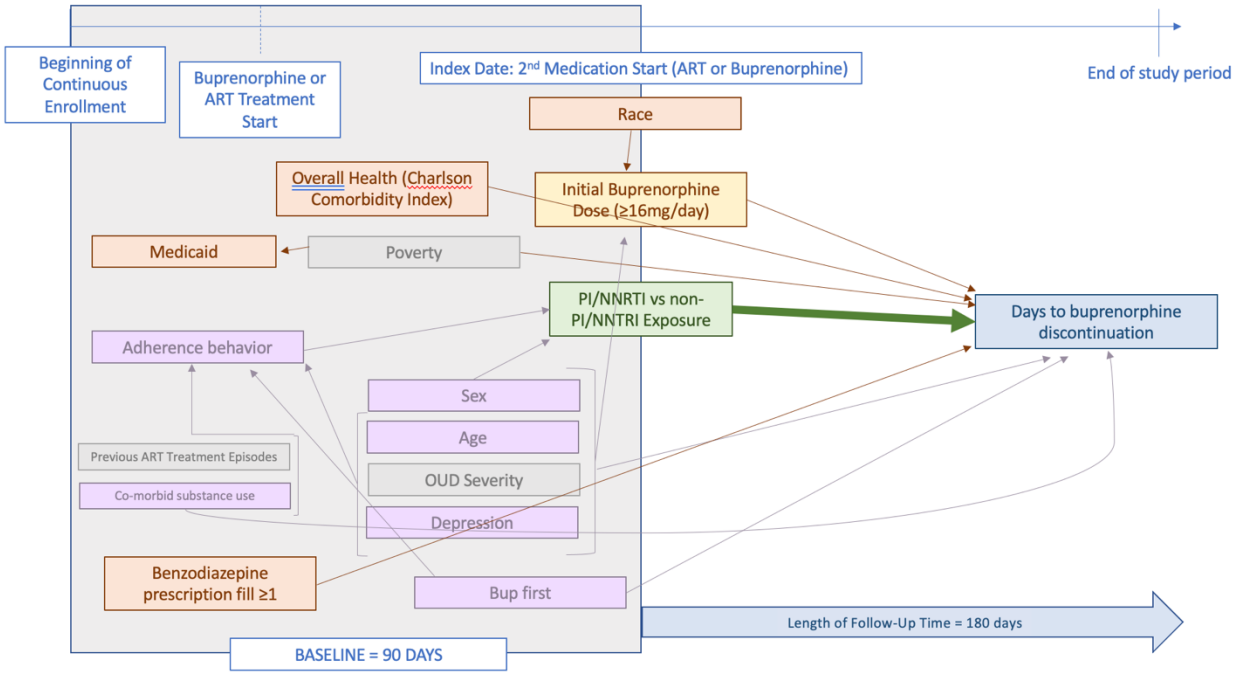
Buprenorphine Daily Dose Mismeasurement Correction

Three people had daily estimated doses of buprenorphine that were below 2mg/day. This dose is well below therapeutic levels and is unlikely to be correct. Seven people had daily estimated

doses of buprenorphine that were greater than 32mg/day. These doses are well above levels that would be prescribed to the patients. This provided 10 or 6% of people with likely mismeasured levels of buprenorphine in the cohort. Daily estimated doses of buprenorphine were calculated from three variables within the prescription claims data. These variables include the strength of buprenorphine per unit, the number of units supplied by the single prescription, and the days supply this number of units should last the individual. The strength of the medication per unit is auto populated from the National Drug Code (NDC) number selected by the provider. The units supplied and the days' supply are entered by the healthcare provider. Among those eligible for cohort inclusion, all days' supply quantities were within reason (Range: 1-30 days). However, the quantity of units supplied varied substantially and contained unlikely values (Range: 0-750 units). The quantity of units supplied was, thus, selected as the likely source of mismeasurement. To correct this measurement error, the quantity of units supplied among those people with <2mg/day and > 32 mg/day was replaced with the median quantity of units supplied from all commercial and Medicaid buprenorphine claims in MarketScan, stratifying on unit strength, product brand name, and days' supply. For example, there was an individual with a unit strength of 4mg, a quantity supplied of 0.004 units, and a days supply of two days. This led to an estimated daily buprenorphine dose of 0.008mg/day. There were 1,508 prescriptions in the full MarketScan dataset with 4 mg of this form of buprenorphine for two days, and the median quantity supplied was 4. Thus, the units supplied of 0.004 was replaced with 4. All expected daily doses of buprenorphine (mg/day) were ≥2mg/day and ≤32 mg/day after this correction was applied. Mean imputation was not used to avoid the effects of outliers.

Supplementary Figure 3-1: Directed Acyclic Graphs (DAGs)





*Variables surrounded by a small grey box indicate unmeasured variables in the analysis.
*Bup first= buprenorphine was prescribed prior to incident antiretroviral therapy for the treatment of HIV. This also implies that the individual would have a history of buprenorphine adherence.

Chapter 4 Opioid agonist therapy adherence trajectories among people living with Hepatitis C: implications for opioid use disorder treatment retention (Aim 3)

Introduction

Opioid use disorder (OUD) is highly prevalent in the United States. In 2019, an estimated 6-7 million adults and adolescents were living with OUD.[3] The gold standard treatment for OUD is opioid agonist pharmacotherapy involving buprenorphine or methadone-containing medications.[44,133] Despite evidence that buprenorphine and methadone are both safe and effective, treatment adherence and retention are low.[10,134] For example, state-level monitoring has shown that many patients who receive buprenorphine participate in treatment for only 1-2 months.11 Because longer treatment (at least fifteen months) is associated with significantly less hospital use, fewer overdose events, and lower rates of prescription opioid use,[10] addressing medication adherence is crucial to providing lasting benefits to patients.

Hepatitis C virus infection is a major public health concern, with people living with opioid use disorder having a significantly higher risk of infection.[5,135] In 2020, the CDC reported that the majority of new HCV cases (66%) in the US occurred because of injection drug use.[5] In one study of people engaging in office-based buprenorphine therapy for the treatment of OUD, the prevalence of HCV was 48%.[136] Because people living with HCV and OUD, in comparison to OUD alone, have twice the hazard of death and significant morbidity,[33] effectively treating both HCV and OUD is a public health imperative. Crucially, people living with HCV on opioid agonist therapy (OAT) demonstrate a 50% reduction in HCV transmission.[29] Thus, ensuring adequate access and adherence to opioid agonist therapy is vital to reaching HCV elimination.[34]

Despite the cooccurrence of HCV and OUD, little is known about patterns of treatment for OUD in this population. In one previous study examining baseline risk factors associated with buprenorphine non-adherence among Medicaid beneficiaries between 2013-2015, HCV diagnosis was associated with a slight increase in the hazard of discontinuation and lower odds of having buprenorphine treatment for at least 180 days.[10] It is also possible that people who are living with HCV have a different set of risk factors for OAT adherence in comparison to the overall population living with OUD. A previous study examining a population with OUD and HIV found that linkage to the healthcare system through HIV treatment positively impacted OAT receipt.[132] It is reasonable to hypothesize that HCV care would also beneficially impact MOUD care. Understanding patient characteristics related to OAT adherence among people living with HCV is vital to tailoring strategies to improve medication adherence and health outcomes.

The purpose of this study was to characterize OAT adherence trajectories over fifteen months following OAT initiation among people living with HCV and OUD and to investigate baseline demographic, clinical, and healthcare utilization factors associated with these OAT treatment adherence trajectories.

Methods

Study Sample

The Merative MarketScan Commercial and Multi-State Medicaid databases contain information on individual-level paid claims that is longitudinal and linkable between service types and across different health providers and health plans. Claims in the commercial database are populated

from commercial insurance companies with broad geographic coverage. The Multi-State Medicaid data includes data from seven million Medicaid recipients in eleven state Medicaid programs and Medicaid Managed Care programs.

We constructed a retrospective cohort of people diagnosed with OUD and HCV who filled prescriptions for methadone, buprenorphine, or buprenorphine/naloxone between January 1, 2015, and December 31, 2019. The index date or cohort entry date was defined as the start of buprenorphine or methadone therapy. We excluded people who had less than one year of continuous enrollment with prescription drug coverage before the index date to ensure adequate time to define baseline characteristics and to increase the probability of capturing incident OAT treatment. OUD was defined using inpatient and outpatient services and outpatient pharmacy dispensing records.[44] HCV was defined as at least one chronic HCV diagnosis in the baseline period.[137] Acute HCV diagnosis was excluded to increase specificity in identifying HCV cases.[137] We used outpatient pharmacy dispensing records to identify prescription fills for buprenorphine or methadone using their generic names. We excluded buprenorphine formulations not indicated for treating OUD, such as Belbuca and Butrans.

OAT treatment adherence was defined as the number of days a person had OAT supply per 30-days of follow-up, or roughly one month. OAT supply was collected from outpatient pharmacy dispensing records. Adjacent OAT prescriptions were appended to construct OAT continuous use periods. All OAT continuous use periods within 15 30-day periods (30*15=450 days) of OAT initiation were included in the analysis. Fifteen variables were then constructed indicating the number of days in the 30-day period the person had OAT supply.

People were not dropped from the analysis if they did not have 15 months (450 days) of continuous enrollment with prescription drug coverage past cohort entry. Differing lengths of follow-up periods were addressed in the statistical analysis. Missingness in the number of OAT days per month due to the end of continuous insurance enrollment was assumed to be missing at random.

Baseline Characteristics

We measured the following baseline characteristics: age at cohort entry, sex (male vs. female), at least one fill for an HCV DAA medication in the baseline period in outpatient pharmacy dispensing records, HIV diagnosis, chronic pain, cirrhosis, the type of opioid agonist medication initiated (methadone vs. buprenorphine), opioid overdose, non-opioid overdose, substance use other than opioids, depression, anxiety, number of non-emergency outpatient visits, emergency room visits, inpatient admissions, individual or group psychotherapy or counseling, and race (Medicaid cohort only). These measures were selected because they were associated with medication adherence in previous studies.[10,85,138,139] Specific diagnosis and procedure codes used are in the Appendix (Tables S1 and S2).

Statistical Analyses

Growth Mixture Model

To estimate the number and shape of the latent buprenorphine adherence trajectories, we fit growth mixture models (GMM). The GMM specification used in this study is given by[140]

$$y_{it}^{k} = \left(\beta_0^k + b_{0i}^k\right) + \left(\beta_1^k + b_{1i}^k\right)X_{it} + \left(\beta_2^k + b_{2i}^k\right)X_{it}^2 + \left(\beta_3^k + b_{3i}^k\right)X_{it}^3 + \varepsilon_{it}^k$$

Where t=1, …, T denotes time (month), i=1…, N denotes individual, and y_{it} denotes the number of days of OAT medication during month t for individual i. k=1,…, K denotes latent class.[140,141] β_0^k, β_1^k, β_2^k, and β_3^k are fixed effects specific to latent class k. β_0^k is the class-specific intercept. β_1^k, β_2^k, and β_3^k are the slope (3rd order polynomial trend over 15 months of follow-up time). b_{0i}^k, b_{1i}^k, b_{2i}^k, b_{3i}^k are the random effects that capture inter-individual variability in the trajectory estimated within class k. ε_{it}^k is the intra-person variability and is class specific. This model lets each group of participants (called a "latent class") have a unique starting point (baseline) for the number of OAT days in a month and a different rate of change (slope) over time, following the initial point.

Within each group, participants can vary from the average starting point and rate of change. Additionally, the amount of variation allowed for each group can differ from one another. Thus, this model accounts for the fact that different groups of patients may adhere to OAT in different ways, both in terms of how much they adhere initially and how their adherence changes over time.

Model Selection and Goodness of Fit

We employed a combination of previously published approaches to selecting the model for latent class analyses.[140–143] We started with a one-class baseline model with a simple slope and intercept ($y_{it} = \beta_0 + \beta_1(X_{it}) + \varepsilon_{it}$). We then increased the polynomial order up to a 3rd-degree polynomial and selected the model with the highest Bayesian information criterion (BIC).

To assess the classification of individuals into classes, we also used scaled entropy and the average posterior probability of assignment (APPA). APPA was used to evaluate group-specific classification certainty. Values of the APPA vary from 0 to 1, and values >0.7 are considered adequate.[140] Scaled entropy is an overall measure of classification certainty. Entropy values range from 0 to 1, and values greater than 0.5 are generally sufficient, and values > 0.8 indicate high classification certainty.[140]

We also fit group-based trajectory models (GBTM) with up to four latent classes. GBTM are like GMM but do not allow interindividual variation within classes (i.e., individual trajectories are homogenous within class). Again, the model with the highest BIC was selected. Group-based trajectory modeling was implemented to obtain starting values for the later GMM models. Obtaining starting values from a model with more simplifying assumptions is a method to increase the likelihood of model convergence in more complex and flexible models.

We then relaxed the homogeneity within class restrictions to fit the GMM. BIC, entropy, the size of the latent classes, and the clinical relevance were then assessed holistically to determine the appropriate number of classes to be used. The polynomial was then rechecked and updated if needed, fixing K at the value specified in the previous step. Observations were weighted by GMM posterior class probabilities to account for uncertainty in class membership.[141] Models were run ten times using different start values to avoid local maxima.[141,144] Class membership was assigned using the three-class GMM by assigning people to the class for which they had the

highest posterior probability of group membership based on their adherence pattern during follow-up.

Analysis of baseline characteristics associated with class membership

We estimated the association between baseline characteristics and OAT adherence trajectory membership over the 15-month follow-up period. We used multinomial logistic regression to calculate unadjusted odds ratios comparing the odds of class membership with the reference class. The class with the lowest mean number of days of OAT was assigned as the reference class.

This study was reviewed by the University of California, Los Angeles (UCLA) Institutional Review Board and deemed not human subjects research. Models were built in R v4.3.2[145] using the 'lcmm' package.[146]

Results

A total of 5,495 people were included in this study. Summary statistics of cohort baseline characteristics are presented in Table 1. At the index date (initiation of OAT therapy), the median age was 36 years (IQR: 29-48), and there were slightly more women than men (females: 53%; males: 46%). Most patients were Medicaid beneficiaries (89%). Among those in Medicaid with race information, the majority were white (68%). People were mostly on buprenorphine (buprenorphine: 95%; methadone: 5%), and 17% of people had recorded history of an opioid or non-opioid overdose. The majority had an additional substance use diagnosis (87%), most commonly tobacco/nicotine products (73%). Over half had comorbid anxiety (55%) and

depression (51%) and 52% received individual or group psychotherapy during the year prior to OAT initiation. In addition to psychiatric diagnoses, 76% of people at baseline had a chronic pain diagnosis. Despite all patients having HCV diagnosis, only 17% of patients had a outpatient pharmacy dispensing record for Hepatitis C direct acting antiviral prescription. Patients also mostly had at least one emergency healthcare visit (79%) or inpatient admission (55%) during the year prior to OAT initiation.

We identified three distinct OAT adherence trajectories. These trajectories were low OAT adherence (Class 1, N=1,904, 35%), moderate OAT adherence (Class 2, N=2,150, 39%), and high OAT adherence (N=1,441, 26%) (Figure 1). The low adherence trajectory was characterized by initial adherence, which quickly reduced to no OAT medication before six months. The moderate adherence group was characterized by initial adherence that gradually reduced to no OAT medication by the end of follow-up (15 months). The high adherence group maintained an OAT supply for the entirety of the fifteen-month follow-up period. The average posterior probability of assignment (APPA) was >0.7 for all classes (Class 1: 0.95; Class 2: 0.90; Class 3: 0.95), and the relative entropy was 0.86, indicating good model classification ability (Figure S1).[140,144]

We selected third-order polynomials for each class to model the predicted number of days covered per month (Figure 1). The mean monthly days of OAT supply by class was 2 days (SD: 7) for the low adherence class, 13 days (SD: 14) for the moderate adherence class, and 26 days (SD: 9) for the high adherence class.

Several baseline covariates were associated with OAT adherence trajectory group membership (Table 2 and Figures S3-S6). Compared to the low adherence group, moderate and high adherence groups were less likely to have other substance use diagnoses and more likely to initiate buprenorphine instead of methadone, be older and female, have hepatitis C direct acting antiviral treatment during baseline, have a greater number of outpatient visits, no emergency or inpatient encounters, and have no baseline overdoses. People with chronic pain at baseline were also more likely to be in the moderate and high adherence classes. Among Medicaid beneficiaries with race information, patients identifying as black were less likely than white patients to be in the moderate and high adherence groups.

Discussion

In this study, we aimed to characterize OAT adherence trajectories over fifteen months following OAT initiation among people living with HCV and OUD. We also examined the extent to which baseline demographic, clinical, and healthcare utilization characteristics were associated with OAT adherence trajectory membership. We identified three distinct adherence trajectories. Notably, 60% of the beneficiaries were classified into sub-therapeutic adherence groups. Both the low and moderate OAT adherence trajectory groups had a mean proportion of days covered per month of less than 50% (<15 days).

There was a dose-response relationship between baseline characteristics and moderate and high adherence trajectory membership versus low adherence membership. Characteristics that were associated with moderate adherence group membership were generally even more strongly associated with membership in the high adherence group. People in the high adherence group

were older, more likely to be women (vs. men), have anxiety, chronic pain, baseline hepatitis C treatment, and had the lowest prevalence of non-opioid substance use diagnoses, including tobacco. People in the high adherence group also had significantly fewer inpatient admissions and emergency visits in the year prior to buprenorphine/methadone initiation. People in the moderate adherence group was very similar but with less pronounced differences in comparison to the low adherence group. These results are consistent with previous studies examining correlates of MOUD adherence among individuals without HCV.[10,85,147] We contributed to this literature by examining associations among people living with HCV and characterizing adherence into adherence trajectories instead of static outcome measures.

Troublingly, people in all three groups experienced high levels of both opioid-related and non-opioid-related overdoses in the year prior to buprenorphine/methadone initiation. Overall, nearly one in five members of the cohort had an overdose during the baseline period. There was variation in prevalence of overdoses at baseline between the three adherence groups. People in the low adherence had the highest prevalence of opioid and non-opioid overdoses at baseline (opioid-related: 20%; non-opioid-related: 19%), while people in the high adherence group had the lowest (opioid-related: 14%; non-opioid-related: 14%). However, all overdose prevalence estimates were high (>10%).

Younger age and male sex have been linked to lower adherence to buprenorphine.[10,148–150] Differences in executive functioning among younger adults may explain earlier dropout from addiction treatment,[151] thus opioid treatment programs designed to treat young adults are particularly needed. Several explanations have been suggested for lower buprenorphine

adherence among men. For example, women may be exposed to higher levels of buprenorphine at the same doses, given sex-specific pharmacokinetic differences.[152] It is, however, unclear how much this is dose-dependent.[152] Second, the prevalence of depression is higher among females, and buprenorphine may have antidepressant effects.[153,154] Previous researchers have suggested buprenorphine's potential to alleviate depression among women as an additional explanation for higher female OAT adherence.[10] However, other studies have supported depression as a risk factor for early OAT discontinuation.[155] Future research exploring sex-specific pharmacokinetics and depression may further illuminate the association between sex and OAT adherence.

Like prior research, the present study found an association between black race and low OAT adherence. Previous research has shown that minority groups in the United States may have systematically worse access to medication for opioid use disorder, particularly buprenorphine therapy, and that they often must travel further to access treatment centers.[149,156,157] This is particularly troubling because opioid overdoses are increasing at the fastest rate among black Americans,[158] and this disparity may have been exacerbated by the COVID-19 pandemic.[159] Further research into how best to reduce systemic barriers to OAT retention among Black Americans is imperative. Policies to expand Medicaid coverage, allow remote buprenorphine induction via telehealth therapy, and enable methadone dispensation in office-based practices may help address inequities in care.[160]

Non-opioid substance use is common among people living with OUD.[161] People often combine opioids with other substances to self-medicate to treat opioid withdrawal or cocaine overstimulation and to alter or enhance substance-induced euphoria.[161] In the present study,

people with a history of non-opioid substance use in addition to OUD were more likely to be in the low adherence group than other groups. The presence of multiple substance use disorders is associated with a more severe clinical course over time in comparison to those with only one substance use disorder.[162] Even below disordered levels, the use of additional substances can lead to reduced retention in OAT therapy.[161] The present findings are particularly worrisome because use or abuse of respiratory depressants such as alcohol and sedatives in conjunction with buprenorphine and methadone increases the risk of severe adverse events, such as coma and death, due to OAT.[163] These results emphasize the importance of treatment for all relevant substances at OAT initiation.[164]

There is little research on the relationship between anxiety and OAT adherence. Two previous studies have not supported a link between anxiety or anxiety sensitivity and lower OAT adherence.[165,166] However, studies of adherence to other types of medication treatment show superior adherence among those with an anxiety diagnosis.[167] In another study, patients who screened positive for anxiety symptoms on self-administered surveys reported visiting primary care providers more often than those who screened negative for anxiety symptoms.[168] Further research is needed to evaluate the role of anxiety in OAT treatment adherence.

Previous research has focused on the effect of OAT therapy adherence on HCV DAA adherence.[169–171] As an extension of their primary analysis examining the causal effect of OAT on HCV DAA adherence, Min et al.,[169] examined whether HCV DAA adherence impacts OAT adherence.[169] Contrary to the results of the present study, HCV DAA therapy was not associated with superior buprenorphine adherence.[169] Min et al.,[169] however, used data from an older and

more OAT-experienced population (median age: 52; percentage of cohort with prior OAT: 83%). The relationship between HCV DAA initiation, HCV DAA therapy, and OAT adherence may be different, and older age and experience in OAT treatment may modify this relationship.

HCV DAA therapy may also be a proxy for the quality of healthcare in general. HCV DAA therapy is the gold standard treatment for patients with HCV, and it is recommended that all patients with HCV be treated with HCV DAA. Lack of baseline HCV treatment may indicate poorer overall healthcare quality, which may be associated with poorer OAT adherence.[134]

The positive association between Medicaid coverage in comparison to commercial insurance coverage and high adherence trajectory membership was unexpected. People with Medicaid insurance, on average, have lower income, experience more unemployment, are less likely to have completed high school, and have a higher burden of chronic health conditions in comparison to privately insured people.[172] Lower medication adherence for chronic conditions among people living in low socioeconomic conditions has been noted.[173,174] However, Medicaid insurance is a proxy for socioeconomic status and different prior authorization, formulary, and health coverage policies that vary from state to state. Future research should disentangle these factors to analyze the difference in OAT adherence between people with HCV and OUD who have public vs. private insurance.

We found that patients on methadone were more likely to be in the low adherence group than buprenorphine patients. In contrast, a randomized controlled trial found positive associations between methadone use and medication adherence.[175] Potential explanations for these different

findings may be due to the observational nature of the present study, where patients on who initiated methadone therapy instead of buprenorphine therapy may have had systematically lower probability of adherence at baseline. For example, people with more severe opioid use disorder may have lower baseline probability of adherence and may be disproportionately prescribed methadone.[176]

A previous study examined trajectories of buprenorphine therapy for the treatment of opioid use disorder in the Pennsylvania Medicaid program from 2007-2012.[148] The previous study used GBTM, which has stricter interindividual variation assumptions, likely leading to differing class estimations. The study identified six buprenorphine adherence trajectories. Trajectories were characterized by discontinuation after <3 months, 3-5 months, 5-8 months, >8 months, persistent refills, and intermittent refills. Despite the differing number of groups and underlying statistical latent class model, the shape of the trajectories is consistent with the estimates from our study. Over half of both study populations had adherence trajectories with relatively low OAT coverage. Thus, results from latent class growth analyses are consistent with previous research that has included static adherence measures.

We used latent growth curve analysis to allow for heterogeneity in OAT adherence over the follow-up period. In contrast, single-group multilevel models assume that all people follow the same trajectory over follow-up with inter-individual variability around parameter estimates. This assumption is often not warranted and is relaxed in GMM analyses. Latent growth curve analysis also does not require pre-specifying the number of trajectory groups. Together, latent class

growth analysis models allow for a more nuanced exploration of OAT adherence changes in people living with HCV over time.

The present study also utilizes administrative healthcare claims data to assess OAT adherence trajectories and predictors of trajectory membership. Only information captured for insurance reimbursement would be captured in these data. If OAT medication is paid for by a federal, state, or local grant or cash, our data will not capture this. However, insurance payment is the most common form of payment for OAT.[177] Additionally, the expense of HCV DAA makes it unlikely that DAA therapy was paid in cash.[178] We also did not have information on people's legal, housing, or social issues, which may be important factors in examining medication adherence. These claims data are also nationally sourced but may not be nationally representative of the population living with OUD and HCV on OAT. Results should not be extrapolated to populations without insurance without additional assumptions.

Further, individuals were missing outcome information for some time points if they lost prescription drug coverage during the 15-month follow-up period. Because growth mixture model methods use data in the long format, people with some months of missing adherence information were not dropped. Adherence trajectory may be misclassified due to this missing data. Growth mixture models extrapolate the adherence trend for missing data from non-missing observations. Future studies using data from cohorts that do not use insurance claims data (e.g., electronic health records) can investigate if these results change when data are not missing due to prescription drug coverage termination.

Conclusion

In summary, we have found evidence that there is heterogeneity in OAT adherence trajectories over fifteen months following OAT initiation. Baseline demographic characteristics, healthcare utilization, and psychiatric co-morbidities were associated with membership in specific adherence trajectories. These results can be used to target support for populations with elevated baseline risk of low OAT adherence during follow-up treatment.

Tables and Figures

Table 4-1: Characteristics of the cohort at cohort entry (January 1, 2015 – December 31, 2019), by predicted adherence trajectory.

	Total	Low Adherence	Moderate Adherence	High Adherence
	N=5,495	N=1,904	N=2,150	N=1,441
Age at Index Date, median (IQR)	36 (29-48)	35 (28-47)	36 (29-48)	37 (31-50)
Age (categorical), n (%)				
<25	420 (100%)	172 (41%)	166 (40%)	82 (20%)
25-34	2,037 (100%)	731 (36%)	788 (39%)	518 (25%)
35-44	1,352 (100%)	462 (34%)	532 (39%)	358 (26%)
45-54	848 (100%)	276 (33%)	333 (39%)	239 (28%)
55+	838 (100%)	263 (31%)	331 (39%)	244 (29%)
Sex, n (%)				
Male	2,573 (100%)	961 (37%)	996 (39%)	616 (24%)
Female	2,922 (100%)	943 (32%)	1,154 (39%)	825 (28%)
Race (Medicaid only) , n (%)				
White	3,725 (100%)	1,240 (33%)	1,454 (39%)	1,031 (28%)
Black	381 (100%)	149 (39%)	145 (38%)	87 (23%)
Hispanic	55 (100%)	17 (31%)	18 (33%)	20 (36%)
Other	49 (100%)	-	-	-
Missing	1,285 (100%)	484 (38%)	504 (39%)	297 (23%)
Insurance Source (Ref: Commercial) , n (%)				
Commercial	588 (100%)	218 (37%)	252 (43%)	118 (20%)
Medicaid	4,907 (100%)	1,686 (34%)	1,898 (39%)	1,323 (27%)
Opioid Agonist Type (Ref: Buprenorphine) , n (%)				

Buprenorphine	5,200 (100%)	1,761 (34%)	2,045 (39%)	1,394 (27%)
Methadone	295 (100%)	143 (48%)	105 (36%)	47 (16%)
Any Additional Substance Use, n (%)				
No	713 (100%)	182 (26%)	283 (40%)	248 (35%)
Yes	4,782 (100%)	1,722 (36%)	1,867 (39%)	1,193 (25%)
Alcohol, n (%)				
No	4,030 (100%)	1,357 (34%)	1,570 (39%)	1,103 (27%)
Yes	1,465 (100%)	547 (37%)	580 (40%)	338 (23%)
Cannabis, n (%)				
No	4,032 (100%)	1,307 (32%)	1,594 (40%)	1,131 (28%)
Yes	1,463 (100%)	597 (41%)	556 (38%)	310 (21%)
Cocaine, n (%)				
No	3,960 (100%)	1,263 (32%)	1,573 (40%)	1,124 (28%)
Yes	1,535 (100%)	641 (42%)	577 (38%)	317 (21%)
Hallucinogen, n (%)				
No	5,454 (100%)	1,886 (35%)	2,134 (39%)	1,434 (26%)
Yes	41 (100%)	-	-	-
Inhalants, n (%)				
No	5,438 (100%)	1,880 (35%)	2,129 (39%)	1,429 (26%)
Yes	57 (100%)	24 (42%)	21 (37%)	12 (21%)
Sedatives or Hypnotics, n (%)				
No	4,705 (100%)	1,601 (34%)	1,843 (39%)	1,261 (27%)
Yes	790 (100%)	303 (38%)	307 (39%)	180 (23%)
Other Stimulants, n (%)				
No	4,364 (100%)	1,427 (33%)	1,721 (39%)	1,216 (28%)
Yes	1,131 (100%)	477 (42%)	429 (38%)	225 (20%)
Tobacco/Nicotine, n (%)				
No	1,479 (100%)	449 (30%)	577 (39%)	453 (31%)
Yes	4,016 (100%)	1,455 (36%)	1,573 (39%)	988 (25%)
Other Substance Use Diagnosis, n (%)				
No	2,850 (100%)	897 (31%)	1,135 (40%)	818 (29%)
Yes	2,645 (100%)	1,007 (38%)	1,015 (38%)	623 (24%)
Anxiety, n (%)				
No	2,494 (100%)	907 (36%)	978 (39%)	609 (24%)
Yes	3,001 (100%)	997 (33%)	1,172 (39%)	832 (28%)
Bipolar Disorder, n (%)				
No	3,978 (100%)	1,383 (35%)	1,576 (40%)	1,019 (26%)
Yes	1,517 (100%)	521 (34%)	574 (38%)	422 (28%)

Depression, n (%)				
No	2,691 (100%)	960 (36%)	1,015 (38%)	716 (27%)
Yes	2,804 (100%)	944 (34%)	1,135 (40%)	725 (26%)
Post-Traumatic Stress Disorder, n (%)				
No	4,540 (100%)	1,565 (34%)	1,768 (39%)	1,207 (27%)
Yes	955 (100%)	339 (35%)	382 (40%)	234 (25%)
Schizophrenia, n (%)				
No	5,092 (100%)	1,761 (35%)	2,000 (39%)	1,331 (26%)
Yes	403 (100%)	143 (35%)	150 (37%)	110 (27%)
Non-Opioid Overdose, n (%)				
No	4,539 (100%)	1,539 (34%)	1,758 (39%)	1,242 (27%)
Yes	956 (100%)	365 (38%)	392 (41%)	199 (21%)
Opioid Overdose, n (%)				
No	4,554 (100%)	1,525 (33%)	1,788 (39%)	1,241 (27%)
Yes	941 (100%)	379 (40%)	362 (38%)	200 (21%)
Chronic Pain, n (%)				
No	1,297 (100%)	478 (37%)	511 (39%)	308 (24%)
Yes	4,198 (100%)	1,426 (34%)	1,639 (39%)	1,133 (27%)
HIV, n (%)				
No	5,368 (100%)	1,859 (35%)	2,100 (39%)	1,409 (26%)
Yes	127 (100%)	45 (35%)	50 (39%)	32 (25%)
Cirrhosis, n (%)				
No	4,986 (100%)	1,741 (35%)	1,943 (39%)	1,302 (26%)
Yes	509 (100%)	163 (32%)	207 (41%)	139 (27%)
Baseline HCV DAA Fill, n (%)				
No	4,548 (100%)	1,664 (37%)	1,800 (40%)	1,084 (24%)
Yes	947 (100%)	240 (25%)	350 (37%)	357 (38%)
Individual/Group Psychotherapy or Counseling, n (%)				
No	2,658 (100%)	911 (34%)	1,050 (40%)	697 (26%)
Yes	2,837 (100%)	993 (35%)	1,100 (39%)	744 (26%)
Non-Emergency Outpatient Visits, categorical, n (%)				
<50	2,415 (100%)	939 (39%)	872 (36%)	604 (25%)
50-99	1,461 (100%)	439 (30%)	607 (42%)	415 (28%)
100+	1,619 (100%)	526 (32%)	671 (41%)	422 (26%)
>0 Inpatient Admissions, n (%)				
No	2,454 (100%)	712 (29%)	979 (40%)	763 (31%)
Yes	3,041 (100%)	1,192 (39%)	1,171 (39%)	678 (22%)

>0 Emergency Room Visits, n (%)				
No	1,148 (100%)	374 (33%)	437 (38%)	337 (29%)
Yes	4,347 (100%)	1,530 (35%)	1,713 (39%)	1,104 (25%)

Table 4-2: Odds ratios comparing the association between characteristics of interest and OAT adherence trajectory group membership among people living with Hepatitis C and OUD on OAT. (Reference= Low Adherence Group)

	Moderate Adherence	High Adherence
Demographics		
Age at cohort entry, years		
<25	1	1
25-34	1.09 [0.86,1.38]	1.54 [1.15,2.05]
35-44	1.17 [0.91,1.50]	1.68 [1.24,2.26]
45-54	1.2 [0.92,1.57]	1.88 [1.37,2.59]
55+	1.27 [0.97,1.67]	1.99 [1.45,2.74]
Sex		
Male	1	1
Female	1.20 [1.06,1.36]	1.38 [1.20,1.59]
Race (Medicaid Only)		
White	1	1
Black	0.82 [0.65,1.05]	0.71 [0.53,0.93]
Hispanic	0.96 [0.49,1.87]	1.42 [0.74,2.74]
Other	1.80 [0.94,3.46]	0.43 [0.16,1.16]
Insurance Source		
Commercial	1	1
Medicaid	1.03 [0.84,1.25]	1.54 [1.21,1.95]
Type of OAT Therapy		
Buprenorphine	1	1
Methadone	0.62 [0.48,0.80]	0.39 [0.28,0.55]

Substance Use		
Any additional substance use	0.69 [0.56,0.84]	0.50 [0.41,0.62]
Alcohol	0.92 [0.80,1.06]	0.76 [0.65,0.89]
Cannabis	0.75 [0.66,0.87]	0.60 [0.51,0.70]
Cocaine	0.72 [0.63,0.82]	0.55 [0.47,0.65]
Hallucinogen	0.76 [0.38,1.51]	0.40 [0.16,0.99]
Inhalants	0.79 [0.43,1.43]	0.65 [0.32,1.31]
Sedatives or Hypnotics	0.88 [0.74,1.05]	0.75 [0.61,0.91]
Other Stimulants	0.71 [0.61,0.82]	0.53 [0.44,0.63]
Tobacco/Nicotine	0.84 [0.72,0.97]	0.66 [0.57,0.77]
Other Substance Use Diagnosis	0.79 [0.70,0.90]	0.68 [0.59,0.78]
Opioid Overdose	0.81 [0.69,0.95]	0.64 [0.53,0.78]
Non-Opioid Overdose	0.92 [0.78,1.08]	0.66 [0.54,0.79]
Mental Health		
Anxiety	1.08 [0.95,1.23]	1.25 [1.09,1.43]
Bipolar Disorder	0.95 [0.83,1.09]	1.09 [0.94,1.27]
Depression	1.13 [1.00,1.28]	1.03 [0.90,1.19]
Post-Traumatic Stress Disorder	1 [0.85,1.18]	0.89 [0.74,1.08]
Schizophrenia	0.89 [0.70,1.13]	0.98 [0.75,1.27]
Other Conditions		
Chronic Pain	1.08 [0.93,1.24]	1.24 [1.05,1.46]
HIV	0.96 [0.64,1.46]	0.93 [0.59,1.48]
Cirrhosis	1.13 [0.91,1.41]	1.12 [0.88,1.42]

Hepatitis C Treatment		
Baseline DAA Fill	1.32	2.27
	[1.11,1.58]	[1.89,2.72]
Healthcare Utilization		
Individual/Group Psychotherapy or Counseling	0.96	0.97
	[0.85,1.09]	[0.85,1.12]
Non-Emergency Outpatient Visits		
<50	1	1
50-99	1.5	1.49
	[1.28,1.75]	[1.26,1.76]
100+	1.36	1.24
	[1.17,1.58]	[1.05,1.46]
Inpatient Admissions (yes/no)	0.7	0.52
	[0.62,0.80]	[0.45,0.60]
Emergency Visits (yes/no)	0.96	0.8
	[0.82,1.12]	[0.68,0.95]
Observations	5495	5495

Exponentiated coefficients; Ref= Reference group
95% confidence intervals in brackets; p-values in parentheses.

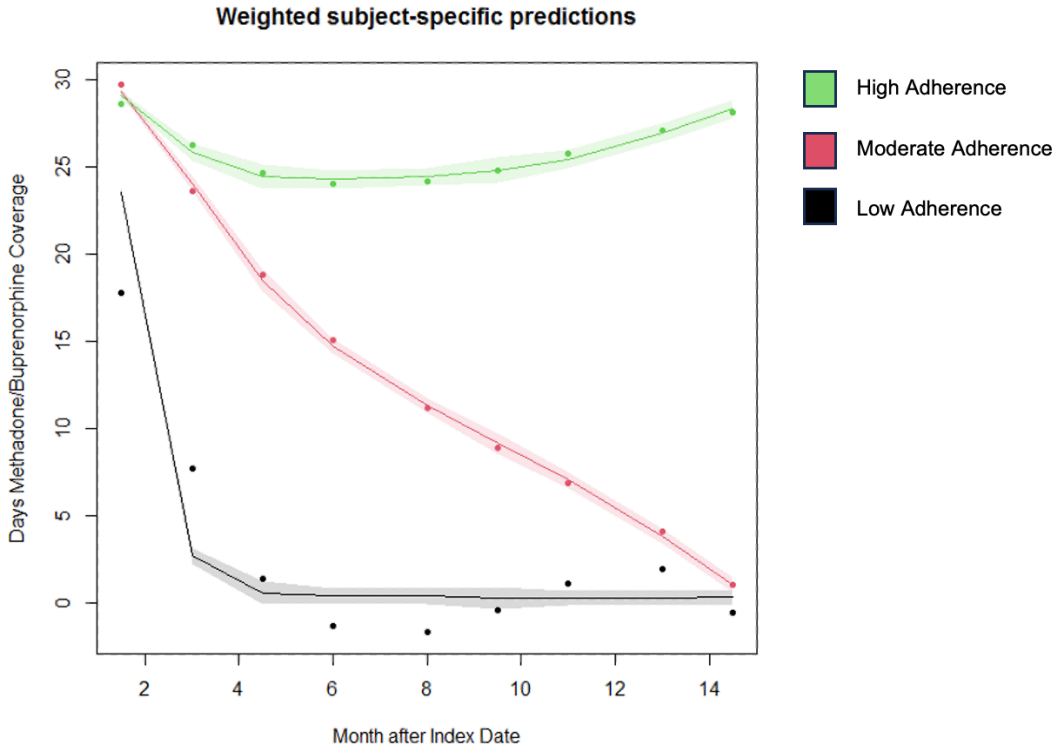
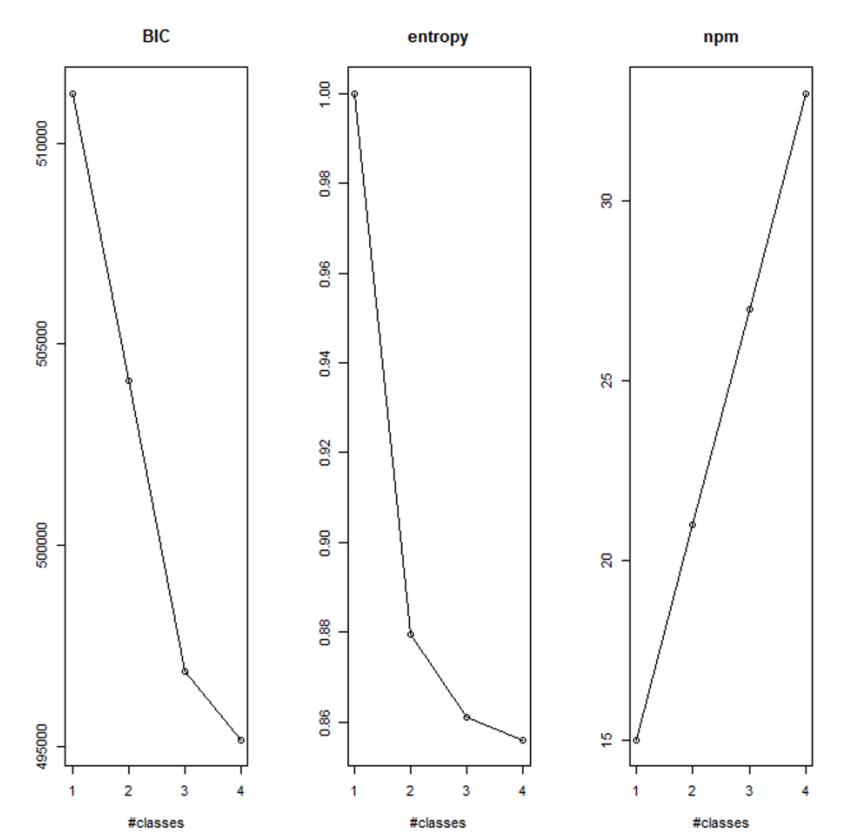


Figure 4-1: Opioid agonist treatment (OAT) adherence trajectories among 5,495 people living with Hepatitis C and OUD (2015 – 2019).

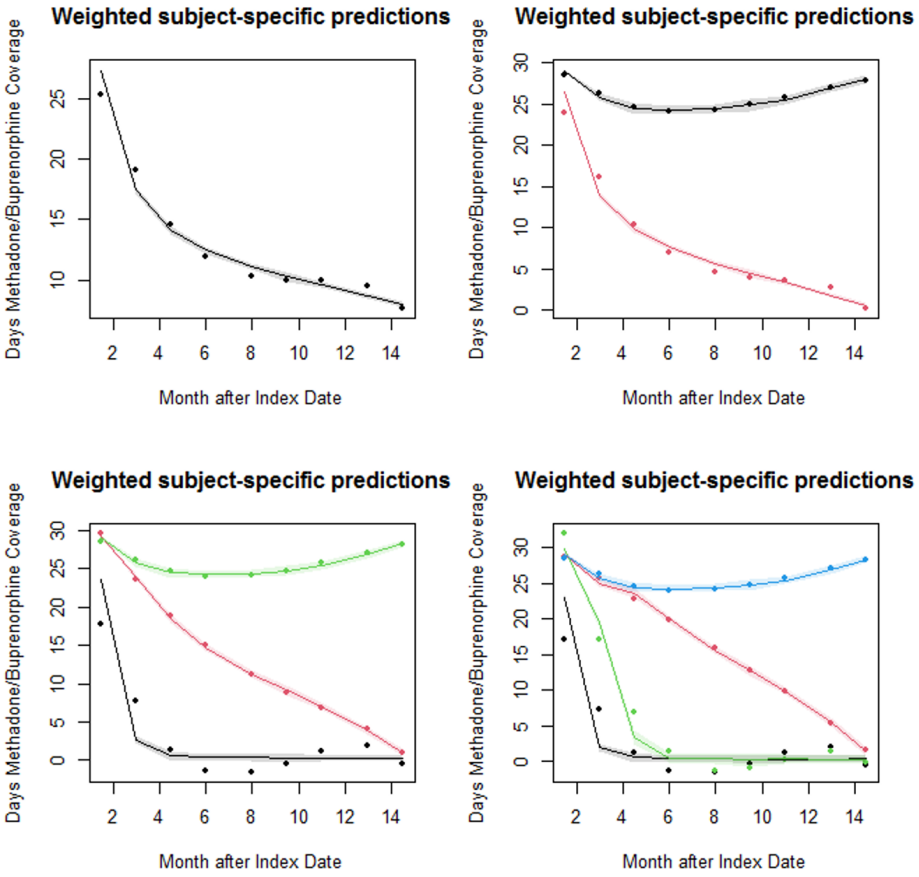
Groups represent people who exhibited low OAT adherence (Class 1, N=1,904, 35%), moderate OAT adherence (Class 2, N=2,150, 39%) and high OAT adherence (N=1,441, 26%) trajectories over time.

Appendix

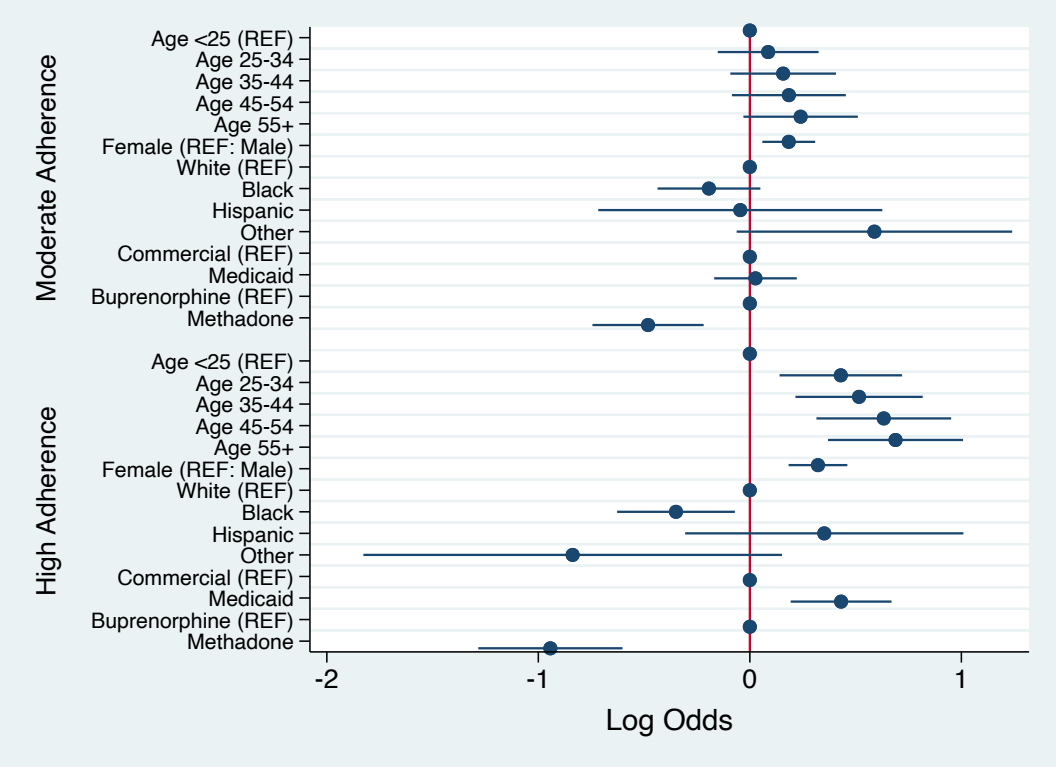


Supplementary Figure 4-1: Post growth mixture model (GMM) estimation statistics.

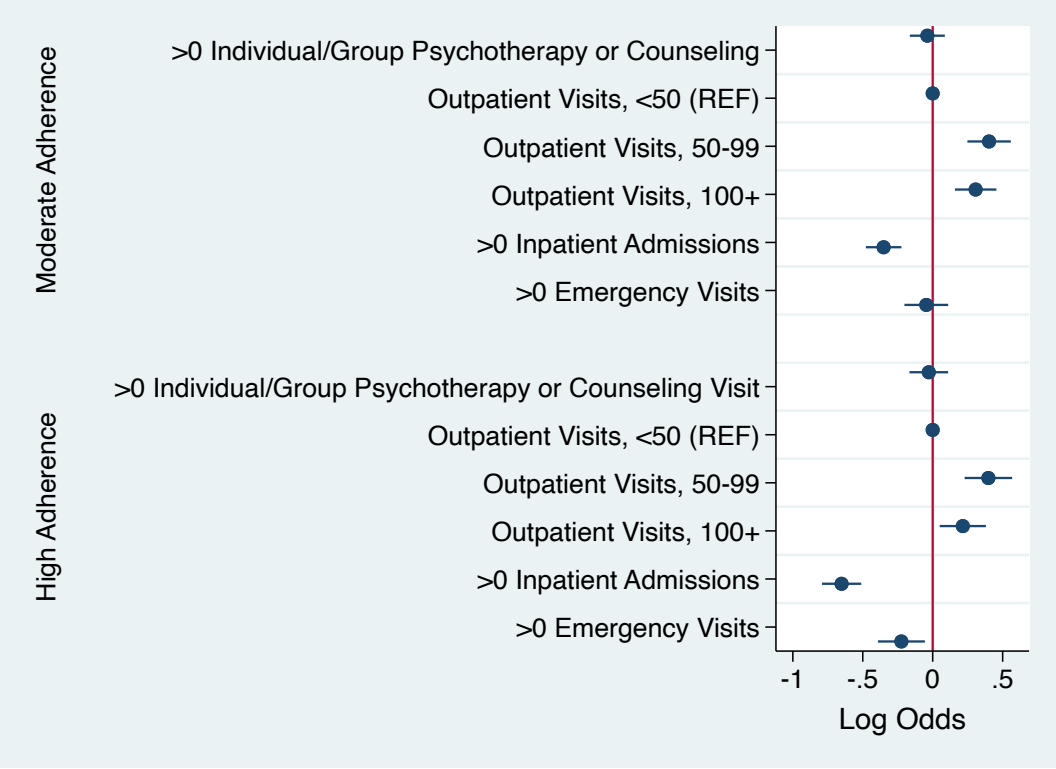
BIC= Bayesian Inference Criterion; npm= Number of Estimated Parameters



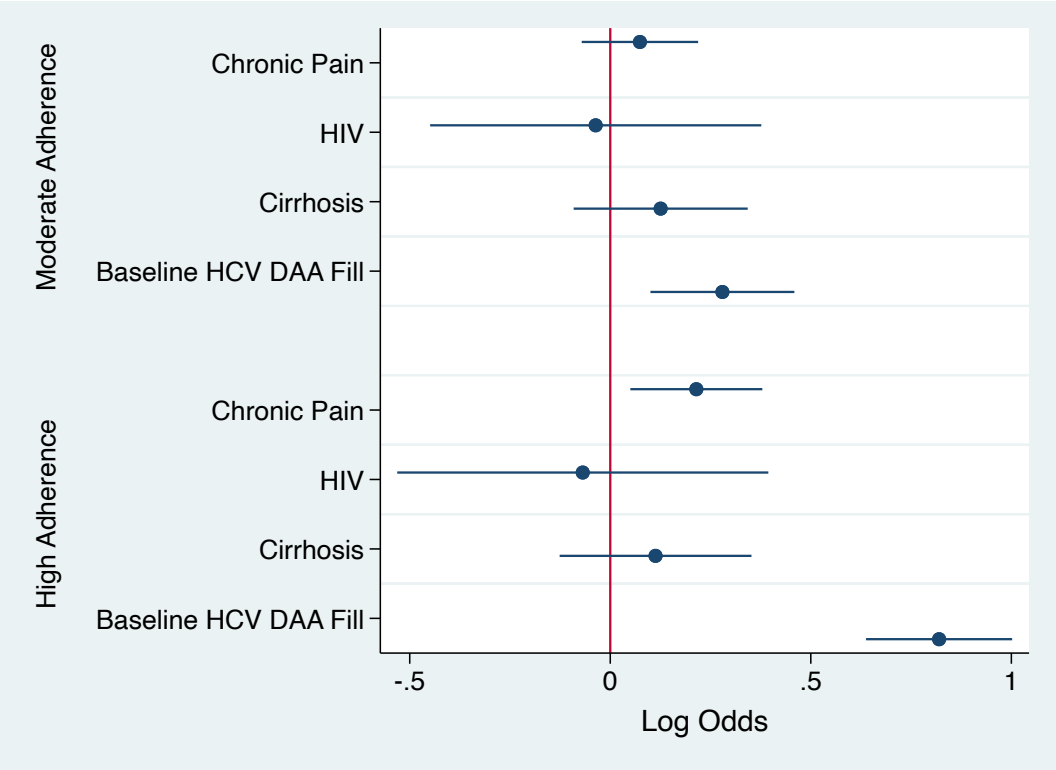
Supplementary Figure 4-2: Opioid agonist treatment (OAT) adherence trajectories among 5,495 people living with Hepatitis C and OUD (2015 – 2019). Models with 1-4 Classes.



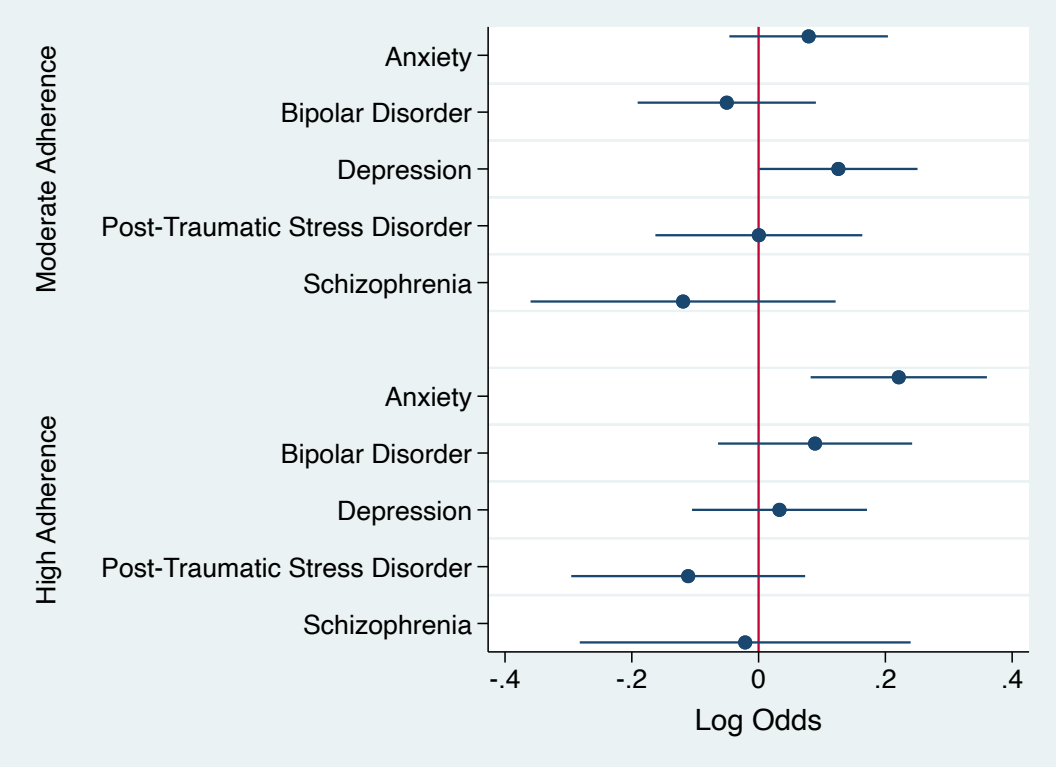
Supplementary Figure 4-3: Log odds ratios comparing the association between demographic characteristics and OAT adherence trajectory group membership among people living with Hepatitis C and OUD on OAT. (Reference= Low Adherence Group)



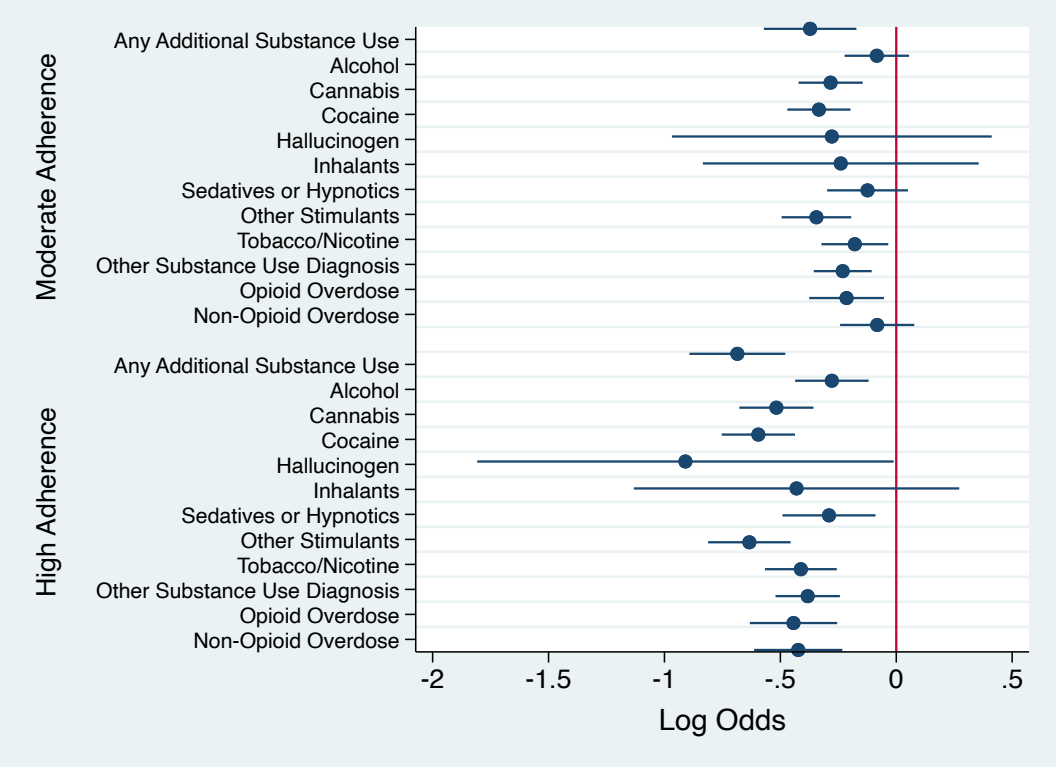
Supplementary Figure 4-4: Lod odds ratios comparing the association between healthcare utilization and OAT adherence trajectory group membership among people living with Hepatitis C and OUD on OAT. (Reference= Low Adherence Group)



Supplementary Figure 4-5: Log odds ratios comparing the association between health conditions and OAT adherence trajectory group membership among people living with Hepatitis C and OUD on OAT. (Reference= Low Adherence Group)



Supplementary Figure 4-6: Log odds ratios comparing the association between mental health diagnoses and OAT adherence trajectory group membership among people living with Hepatitis C and OUD on OAT. (Reference= Low Adherence Group)



Supplementary Figure 4-7: Log odds ratios comparing the association between substance use diagnoses and OAT adherence trajectory group membership among people living with Hepatitis C and OUD on OAT. (Reference= Low Adherence Group)

Supplementary Table 4-1: Medication Codes

Variable	Non-proprietary Names
HCV Direct Acting Antiviral	daclatasvir, dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, simprevir, sofosbuvir+ribavirin, sofosbuvir/velpatasvir, or sofosbuvir/velpatasvir/voxilprevir

Supplementary Table 4-2: Diagnosis Codes

Variable	Code
Depression	ICD: 2962, 2963, 3004, 311, F32, F33, F341
Anxiety	ICD: 3000, 3002, 3003, F40, F41, F42
Post-Traumatic Stress Disorder	ICD: 30981, F431
Bipolar Disorder	ICD: 2960, 2961, 2964, 2965, 2966, 2967, 2968, F31, F340

Schizophrenia	ICD: 295, F20, F21, F25
Additional substance use	ICD: 291, 303, 3050, F10, 3041, 3042, 3043, 3044, 3045, 3046, 3048, 3049, 3052, 3053, 3054, 3056, 3057, 3058, 3059, F12, F13, F14, F15, F16, F17, F18, F19, T405, T407, T409, T42
Chronic Pain	ICD: 30781, 337, 3371, 338, 3382, 3384, 339, 346, 3502, 354, 3544, 355, 356, 357, 377, 710-739, 7840, E0842, E0942, E1042, E1142, E1342, G43, G44, G501, G560, G564, G57, G589, G60, G61, G62, G63, G64, G65, G890, G892, G894, G900, G990, H46, H47, M00-M99, R262, R294, R29898, R51
Overdose	ICD: 9650, E8500, E8501, E8502, T400, T401, T402, T403, T404, 960, 961, 962, 963, 964, 9651-979, E8503, E8504, E8505, E8506, E8507, E8508, E8509, E851-E858, E9500, E9501, E9502, E9503, E9504, E9505, E9620, E9800, E9801, E9802, E9803, E9804, E9805, T36, T37, T38, T39, T406, T407, T408, T409, T41, T42, T43, T44, T45, T46, T47, T48, T49, T50
Individual/Group Psychotherapy or Counseling	CPT: 943, 944, GZ5, GZ6, GZ7, HZ3, HZ4, HZ5, HZ6, 90785, 90832, 90833, 90834, 90836, 90837, 90838, 90839, 90840, 90845, 90846, 90847, 90849, 90853 HCPC: G0409, G0410, G0411, H0004, H0005, H0038, H2027, T1006

ICD: International Classification of Diseases; CPT: Current Procedural Terminology: HCPC: Healthcare Common Procedure Coding System

Chapter 5 Conclusion and Public Health Implications

OUD, hepatis C (HCV), and HIV are components of a syndemic in the US.[4] Both the World Health Organization and the US Department of Health and Human Services (HHS), aim to end the HIV and HCV epidemics by 2030.[7,179] We will not reach these goals unless the complex interactions between the opioid crisis and HCV and HIV treatment are addressed.[6,7] The studies in the present dissertation demonstrated the demographic and clinical predictors of HCV direct

acting antiviral early discontinuation among those on opioid agonist therapy (OAT), predictors of OAT adherence patterns among those with HCV and OUD, and the lack of interaction between HIV treatment and buprenorphine, an OAT medication. These findings can be used to improve clinical guidelines for HIV treatment choice among those with OUD and help to target additional support for patients at increased risk of treatment non-adherence among people with OUD and HCV. Additionally, these results can be used to construct policy to better enable people to adhere to their OUD and HCV treatment.

In our first study (Chapter 2), we investigated patient characteristics and predictors of early DAA treatment discontinuation in a cohort of over 2,000 insured adults on MOUD who initiated HCV DAA therapy between 2015 and 2019. Younger age, psychiatric comorbidities, and later year of initiation were associated with an increased risk of early HCV DAA discontinuation, regardless of type of insurance. Patients had high levels of psychiatric comorbidities, co-occurring substance use, and chronic liver disease. Despite having high levels of potential risk factors for early discontinuation, the overall proportion of people who discontinued HCV DAA therapy prior to eight weeks was like that observed in populations without OUD. Together, these results suggest that OUD should not be used as exclusionary criteria for payer authorization of these life-saving medications and that younger patients and those with co-occurring substance use and psychiatric co-morbidity should be targeted for additional adherence support during HCV DAA therapy.

In our second study (Chapter 3), we examined whether co-use of antiretroviral therapy protease inhibitors (ART PIs) with buprenorphine led to better buprenorphine treatment adherence among

patients living with HIV and OUD. We also investigated whether co-use of ART PIs with buprenorphine led to equivalent buprenorphine treatment adherence at low doses of buprenorphine than would be required in the absence of PIs. The results of our analyses provided weak to no evidence for the effect of PI exposure on buprenorphine adherence and persistence. This study added to a body of evidence that effective medication treatment of HIV and OUD will not likely be hampered or harmed by medication interactions between PIs and buprenorphine.

In our third study (Chapter 4), we characterized OAT adherence over fifteen months following OAT initiation into three distinct trajectories among people living with HCV and OUD (low, moderate, and high adherence). We also investigated baseline demographic, clinical, and healthcare utilization factors associated with membership in these OAT treatment adherence trajectories. Notably, both the low and moderate OAT adherence trajectory groups had a mean proportion of days covered per month of less than 50% (<15 days), which is likely subtherapeutic. Baseline OUD diagnosis without additional substance use diagnoses, initiating buprenorphine instead of methadone, older age, being female, having a greater number of outpatient visits, and no overdoses were associated with higher adherence during follow-up. Conversely, black race was associated with low adherence group membership. These results highlight the need to reduce systemic barriers to OAT retention among Black Americans and ensure providers are trained to effectively deliver MOUD care to young people and those with co-occurring psychiatric disorders.

In summary, the findings of this dissertation highlight specific populations to target for additional support for adherence on these life-saving medications and may help clinicians to

effectively match patients with OUD to forms of HIV ART. These findings also support the need for policy to address systemic barriers to effective OUD treatment, particularly among Black Americans. Previous studies on OAT adherence have not focused on populations with HCV, HCV DAA adherence using real-world data among those on OAT, or used real-word data to explore potential interactions between OUD and HIV treatment. Our results provide vital and novel information on strategies to address the public health emergency that is the OUD, HCV, and HIV syndemic.

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