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INITIATING HCV TREATMENT WITH DIRECT ACTING AGENTS IN OPIOID AGONIST TREATMENT: WHEN TO START FOR PEOPLE CO-INFECTED WITH HIV?

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Abstract

Background—Direct acting antivirals (DAA) raise the possibility of eliminating Hepatitis C virus (HCV) among people who inject drugs (PWID). However, concerns regarding treatment retention and reinfection challenge implementation efforts. Opioid agonist treatment (OAT) provides an opportunity to engage HCV-positive PWID into DAA-based treatment. Our objective was to identify when OAT adherence sufficiently improved to inform DAA initiation in OAT settings, assuming continuous OAT retention for at least twelve weeks is necessary to complete the DAA treatment course.

Methods—This was a retrospective cohort study of HCV/HIV co-infected PWID from a population-level linked administrative database of people diagnosed and living with HIV in British Columbia, Canada between 01/1996 and 12/2013. We used monthly follow-up data after initial OAT entry and considered the effects of demographics, disease severity, and HIV and OAT treatment characteristics over time on the probability of subsequent OAT retention of 12 weeks, and 8 weeks for sensitivity analysis. We fit a generalized linear mixed model to the overall study population, and on stratified samples of those continuously engaged on combination antiretroviral therapy (≥95% ART adherence). A set of monthly indicator variables (months 1, ..., 7, >7) were included to fulfil the study objective.

Results—Our study included 1427 HCV/HIV co-infected PWID (39.0% female, 68.8% OAT-naïve). The odds of subsequent twelve-week retention in OAT were statistically significantly greater in month 3 versus month 1 (adjusted odds ratio: 1.18; 95% confidence interval: 1.02, 1.37); and the odds of subsequent 8-week retention in OAT were statistically significantly greater in

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Conflict of interest

All authors report no potential conflict of interest. Preliminary results of the study were presented during the HepDart 2015 conference by Dr. Bohdan Nosyk.

month 2 versus month 1 (1.15, 95% CI: 1.02, 1.31). Among continuously ART-adherent individuals, the odds of subsequent twelve-week retention were not statistically significantly greater than in month 1 (month 2: 1.12 (0.82,1.51); month 3: 1.08 (0.79, 1.47); month 4: 1.24 (0.91, 1.71)).

Conclusion—We provide evidence that among HCV/HIV co-infected PWID, those retained in OAT for three or more months had higher odds of completing an additional twelve weeks of OAT, compared to no difference in those already receiving ART. These data may have implications for adherence to DAA therapy and further studies are needed to understand the optimal timing of DAA therapy in PWID receiving and not receiving OAT.

Keywords

Hepatitis C virus; HIV; Opioid agonist treatment; People who inject drugs

INTRODUCTION

Hepatitis C virus (HCV) is a leading cause of liver-related morbidity and mortality, affecting approximately 71.1 million individuals, globally (The Polaris Observatory HCV Collaborators, 2017). In high income countries, most new HCV infections occur among people who inject drugs (PWID), with an estimated incidence of 2–46 infections per 100 person-years (Backmund, Reimer, Meyer, Gerlach, & Zachoval, 2005; Folch et al., 2016; Grebely & Dore, 2011; Hajarizadeh, Grebely, & Dore, 2013; Maher, Li, Jalaludin, Chant, & Kaldor, 2007; Page, Morris, Hahn, Maher, & Prins, 2013; van den Berg et al., 2007). While PWID are disproportionately burdened by HCV (prevalence ranging from 60% to 80%), almost half are unaware of their status (Nelson et al., 2011).

The development of simpler, more tolerable and highly effective direct acting antiviral (DAA) agents has generated optimism for the eradication of HCV (Kardashian & Pockros, 2015). Recent modelling exercises demonstrate that HCV prevalence can be reduced considerably if treatment is scaled-up and targeted to PWID, (Grebely & Dore, 2014; Hellard et al., 2014; Martin et al., 2015, 2013) and international recommendations support HCV treatment with DAA therapy for PWID (Grebely et al., 2015). However, concerns regarding suboptimal adherence to HCV treatment, treatment failure, or subsequent reinfection (Grebely, Oser, Taylor, & Dore, 2013; Harris & Rhodes, 2013; Myles, Mugford, Zhao, Krahn, & Wang, 2011) coupled with restrictions on HCV treatment eligibility pertaining to substance use, (Barua et al., 2015) constrain the impact of new DAA therapies among PWID.

Integrating HCV treatment with opioid agonist treatment (OAT) is a promising strategy to engage and retain PWID with DAA therapy (Keats et al., 2015; Treloar, Newland, Rance, & Hopwood, 2010). Improving outcomes by integrating OAT with HIV care is well established (Low et al., 2016) and the 2016 Recommendations of the International Antiviral Society-USA Panel encourage OAT to help improve antiretroviral (ART) adherence among PWID (Gunthard et al., 2016). Similar observational findings of HCV treatment compliance in OAT settings are currently lacking (Taylor, Swan, & Matthews, 2013) and OAT remains highly restricted in many settings (Des Jarlais, Arasteh, & Gwadz, 2010; Mathers et al.,

2008). However, qualitative research from the Enhanced Treatment for Hepatitis C in Opioid Substitution Settings (ETHOS) prospective observational study in Australia, has demonstrated staff and clients welcome the integration of HCV services into OAT settings, citing the benefits of pre-existing relationships, reduced travel time and costs, recurring opportunities for engagement, and immediacy of care available (Treloar, Rance, & ETHOS Study Group, 2014; Treloar, Rance, Grebely, & Dore, 2013).

The successful integration of HCV treatment in OAT for PWID will be contingent on clinicians initiating HCV courses at a time-point when patients are likely to be retained in OAT for at least twelve weeks. Population-level observational studies demonstrate that although OAT is characterized by frequent treatment interruptions (Marcovitz, McHugh, Volpe, Votaw, & Connery, 2016; Nosyk et al., 2009), treatment retention in OAT improves over successive attempts (Marcovitz et al., 2016; Nosyk et al., 2009), thereby offering an opportunity to engage PWID with DAA therapy. However, it remains unclear what the optimal time point is at which DAA can be initiated following OAT initiation, and how this time-point may differ across sub-groups of PWID. Efforts to identify the optimal start time for DAA are complicated by the limited number of PWID concurrently receiving OAT and DAA, making it difficult to directly observe HCV treatment and retention. DAAs are increasingly being added to insurance drug formularies internationally, but remain out of reach for most PWID (Barua et al., 2015). For example, although DAAs were added to British Columbia's provincial PharmaCare drug insurance formulary in 2015, (Pacific Hepatitis C Network, 2016) and drug use or HIV co-infection do not preclude eligibility for treatment, physicians can restrict access to patients that appear to be at high-risk for non-compliance (Marshall et al., 2016).

However, OAT retention can provide indirect evidence for potential DAA treatment adherence among HCV-infected PWID, either engaged or not engaged in other forms of treatment. While we currently lack population-level data for the entire HCV-infected population of PWID, we may examine OAT retention using linked population-level data available for British Columbia on HIV/HCV co-infected populations initiating OAT. Using this data, we undertook this study to identify when OAT adherence sufficiently improved to inform DAA initiation in OAT settings, assuming continuous OAT retention for at least twelve weeks is necessary to complete a DAA treatment course.

METHODS

Design

We used a population-level retrospective cohort of HIV/HCV co-infected PWID in British Columbia (BC), Canada. The cohort was followed in a unique environment wherein all antiretroviral medications, and approximately 85% of OAT expenses (e.g. physician, drug dispensing, medication and counselling fees) were covered by the province's universal PharmaCare insurance. In fiscal year 2013/14, PharmaCare paid \$46 million of the \$53 million (CAD) associated with OAT, while private insurance and patients paid the balance (Medical Beneficiary & Pharmaceutical Services Division, Population and Public Health Division, & British Columbia Ministry of Health, 2015). Ethics approval for this study was provided by the University of British Columbia and Providence Healthcare.

Data source

This study was based on a provincial-level linkage of seven health administrative databases and disease registries: (1) antiretroviral dispensation, (2) virology and (3) HIV-testing registries (antiretroviral dispensations, plasma viral load (pVL), CD4⁺ cell count tests, nominal HIV diagnoses); and the province's (4) Medical Services Plan (MSP, physician billing records), (5) discharge abstract (hospitalizations), (6) PharmaNet (all non-antiretroviral drug dispensations including OAT), and (7) vital statistics (deaths) databases. Further details regarding the construction of the cohort and available databases are described in detail elsewhere (Nosyk et al., 2013). Since administrative data was used, no informed consent was required from patients in the cohort.

Study population

We restricted our analysis to individuals who sought OAT at any point following HIV diagnosis, determined by dispensation records of OAT (either methadone or medications containing buprenorphine) in the PharmaNet database, from 1 January, 1996 to 31 March, 2014 using unique American Hospital Formulary Service (AHFS) pharmacologic numbers. These codes encompass current and past DINs used for the medications in question and are specific to indications for opioid use disorder, as opposed to pain management. Previous studies have defined methods to clean and process PharmaNet data for accurate estimation of OAT episodes (Nosyk et al., 2009). OAT dispensation record capture was complete for the province of BC.

Individuals were followed until death, administrative loss to follow-up, three months prior to the end of study follow-up (31 December, 2013), or the end of the seventh OAT episode (excluding the few extreme OAT initiators). Administrative loss was defined as no record in any of the linked databases for a period of at least 18 months.

Outcome

The outcome was a time-dependent, monthly-updated binary (yes/no) measure of 100% OAT adherence (i.e. no days of OAT missed) for twelve weeks from the most recent month completed within a given episode of OAT per patient. An episode of OAT was defined as a continuous period of dispensed OAT medication with no more than a month gap between treatments. A new episode of treatment indicated re-initiation of OAT following a month or longer interruption of dispensed OAT medication. Each episode was followed for up to eighteen months, loss to follow-up, death, or censoring. For sensitivity analysis, we changed the duration of adherence from twelve weeks to eight.

Covariates

The primary independent predictor was the consecutively-numbered month on continuous OAT. Other covariates included patient socio-demographics, OAT factors, HIV progression and treatment status, and recent pharmaceutical treatment for mental health and pain management as described below.

Participants' age, sex, and men who have sex with men (MSM) status were defined at the beginning of the OAT episode. Chronic disease score (CDS) was determined using

medication dispensation records (excluding ART dispensations) (Putnam et al., 2002; Von Korff, Wagner, & Saunders, 1992) and updated monthly.

Covariates describing aspects of the course of OAT were per treatment episode and updated monthly. Patients who received any OAT before the current episode were categorized as OAT experienced, including those with OAT receipt prior to HIV diagnosis since our administrative data included all patient records of service use during the study period (1996–2014) regardless of when HIV diagnosis occurred. Similarly, OAT initiated within three days of hospital discharge was defined as ‘hospital initiated’ for that episode. OAT compliance (titration or median effective dose complies with treatment guidelines, e.g. 60 mg for methadone), taper or titration, and change of provider from first assigned provider were assessed at the end of each month within an episode of treatment. For HIV progression and treatment status, time since HIV diagnosis (years), ART adherence 95% for at least three months prior to OAT initiation (yes/no), and ART therapy type (traditional/1st generation, contemporary/2nd generation or multi-drug resistance (MDR) regimens) were set at the beginning of the episode. The most recent CD4 count (missing, <200, 200–349, 350–499, 500) and viral load (detectable or not) within six months, were updated each month.

Individuals recently treated for mental health and/or pain management, were identified using the following DINs prescribed within a year prior to the OAT episode: antidepressants = 281604; antipsychotics or benzodiazepines = 281608, 282800, 281208, and 282408; and opiates for pain management = 280808 or 280812.

Statistical analysis

We conducted bivariate analyses to identify variables for inclusion in the mixed effects regression models. To appropriately account for differences in inter- and intra-group variances, the data was organized into three levels: patient, episode of OAT, and month of treatment within the episode. Generalized linear mixed regression models, with logit link and binomial distribution were used to account for intra-individual correlation between repeated measures and to control for potential unmeasured confounders that were fixed over time.

We restricted ourselves to all patients who were retained in OAT at $t = 1, 2, \dots, 18$ months on the first episode for the prediction time points, and calculated survival probability at twelve weeks for each of these restricted samples with new time origins. We fit a Cox proportional hazards regression model to obtain the adjusted survival probabilities for covariates, using the “DIRADJ” option of the “PHREG” procedure in SAS. We plotted the conditional probability of remaining on OAT for an additional twelve weeks given the number of consecutively elapsed months on treatment (Hieke, Kleber, König, Engelhardt, & Schumacher, 2015). All analyses were executed with SAS version 9.4.

RESULTS

Our cohort included 1427 HIV/HCV co-infected PWID who initiated at least one OAT episode after HIV diagnosis. The cohort had a median number of two OAT episodes per person (IQR = 1–4) for a total of 4062 episodes and 38,137 months of follow-up (median =

eight months, IQR = 2–18) (Table 1). The population was predominately male (61%), and 8% identified as MSM. In the previous year, 42% and 23% of the cohort were prescribed medication to treat a mental health issue or took an opioid for the treatment of pain, respectively. The majority (72%) of the cohort had not started ART at the beginning of OAT.

Within the first episode of OAT, the proportion of individuals retained an additional twelve weeks increased from 20% to 31% between the first and seventh month; while the proportion retained an additional eight weeks increased from 27% to 40% over the same period (Table 2).

The results of the multiple logistic regression are presented in Table 3. After controlling for covariates, the odds of OAT adherence for a subsequent twelve weeks were significantly improved after the third month of OAT (OR_{3rd month} = 1.18, 95% CI: 1.02–1.37); and the odds of OAT adherence for a subsequent eight weeks significantly improved after the second month on OAT (OR_{2nd month} = 1.15, 95% CI: 1.02, 1.31).

Female sex (OR = 0.74, 95% CI: 0.63–0.87) and opiate agonist treatment for pain management (OR = 0.85, 95% CI: 0.74–0.98) were associated with significantly reduced odds of twelve week adherence, while older age was associated with improved odds of adherence (OR = 1.37, 95% CI: 1.26–1.50). Previous OAT experience (OR = 1.38, 95% CI: 1.17–1.62), cumulative OAT adherence >95% (OR = 2.02, 95% CI: 1.86–2.21), and medication to treat mental health (OR = 1.25, 95% CI: 1.07–1.46) were also associated with improved odds of twelve week adherence. Meanwhile MSM status, chronic disease score, AIDS defining illness prior to OAT initiation, CD4 count, OAT initiation during hospitalization, and changes in OAT prescriber were not associated with OAT adherence. With the exception of OAT initiation during hospitalization (OR = 1.15, 95% CI: 1.01–1.30), these findings were repeated when using eight weeks of adherence as the outcome.

To aid in the interpretation of the results from the three-level multiple regression, Fig. 1 is a plot of the conditional probabilities of OAT adherence for an additional twelve weeks after the current month, for an individual on his or her first episode of OAT. The figure was developed using adjusted Cox proportional hazards survival models built with all the covariates listed in Table 3. The figure shows OAT retention for a subsequent twelve weeks improves the longer the patient is on OAT, and that the probability of retention for at least twelve weeks is 85% higher after the third month of OAT adherence on the first episode of treatment. Together with the results of Table 3, this figure shows that the probability of OAT adherence long enough to support HCV treatment is statistically improved in individuals who remain on OAT for at least three months.

When we stratified our model by ART adherence we found that the odds of OAT retention for twelve weeks stayed the same over time in the ART adherent group (episodes of OAT where the patient demonstrated 95% ART adherence in the previous three months) (see Table 4). However, the odds of OAT retention for an additional twelve weeks was significantly higher than at treatment initiation after the third month of OAT (OR_{3rd month} = 1.19, 95% CI: 1.01–1.40) in the group that was not ART adherent for three months prior to the episode. These results are summarized in Table 4 and combined present evidence to

initiate HCV treatment for PWID who demonstrate OAT or ART adherence for at least three months.

DISCUSSION

We used an observational study of OAT retention among HIV/HCV co-infected PWID to identify when OAT adherence sufficiently improved to inform DAA initiation in OAT settings. Our analyses found that after controlling for patient demographics and health characteristics, individuals retained in OAT for three or more months had higher odds of completing another twelve weeks of OAT; individuals retained in OAT for two or more months had improved odds of completing another eight weeks of OAT; and for PWID on ART the odds of completing another twelve weeks of OAT did not change by month. In this context, concurrent retention in ART and OAT appeared to demonstrate ongoing adherence to medical care that could generalize to other forms of continuous care.

Recent post-hoc analyses of data from two DAA trials found there is no difference in completion, adherence, and SVR at twelve weeks between participants with no history of injection drug use (non-users) and PWID on OAT (Grebely, Dore et al., 2016; Grebely, Mauss et al., 2016). While promising, these initial studies were restricted to participants with no substance use in the previous twelve months and clean urine screenings during the trials. However, a trial of 301 DAA treatment-naïve participants with at least 80% adherence to OAT for three or more months expanded on these results (Dore et al., 2016). The study reported drug use during DAA treatment did not affect SVR at twelve weeks and was high for participants who received immediate treatment and those who received treatment after 16 weeks of enrollment (92% for immediate and 90% for delayed treatment, respectively) (Dore et al., 2016). Further, modelling exercises found OAT can reduce the risk of HCV reinfection by 50–80% among PWID in high income countries (Hickman, De Angelis, Vickerman, Hutchinson, & Martin, 2015) and more recently a study of HCV reinfection incidence, risk factors and prevention found OAT was significantly associated with lower risk of reinfection for PWID (Islam et al., 2016). Together, these findings suggest HCV treatment can be integrated with OAT, and OAT adherence long enough to support the standard twelve week DAA regimen has improved significantly by the third month on OAT. Further, they help assuage concerns of suboptimal adherence to HCV treatment, treatment failure, and the development of treatment resistance (Hellard, Sacks-Davis, & Gold, 2009; Martin et al., 2012) which have been used in the past to limit access to DAA for PWID.

In settings such as British Columbia, with a history of integrated HIV and OAT services, these results suggest the integration of HCV care for PWID is ideally positioned to delivery similar success for the HCV epidemic. OAT was de-regulated in 1996 with relaxed constraints on physicians wishing to deliver treatment and the introduction of community-based treatment (i.e. office-based prescription and dispensation in community-based pharmacies) (Brands & Marsh, 1997). These changes saw the number of patients receiving maintenance-oriented OAT increase from 2287 in 1996 to 18,121 in 2013 (British Columbia Office of the Provincial Health Officer, 2013). At the same time, the province expanded access to ART through provincial coverage at no cost to patients (Nosyk, Min, Lima et al., 2015), and funded testing and public health interventions aimed at improving HIV care

(Gustafson, Montaner, & Sibbald, 2012). The combination of OAT and ART expansions with increased access to harm reduction services resulted in decreases in HIV-related morbidity, mortality and transmission (Nosyk, Min, Lima et al., 2015; Nosyk et al., 2017). Furthermore, in this setting characterized by universal healthcare and widespread access to both office-based OAT and ART, OAT among PWID was shown to substantially increase the odds of ART adherence (Nosyk, Min, Colley et al., 2015) and to independently protect against causes of death (Nosyk, Min, Evans et al., 2015). The greatest reductions in mortality were found for PWID receiving both OAT and ART (Nosyk, Min, Evans et al., 2015), suggesting that integrated care may be necessary to achieve maximal impact of HIV and HCV treatment among PWID.

This study was not without limitations. First, we worked exclusively with data on PWID co-infected with HIV/HCV with at least one episode of OAT treatment in British Columbia. This limited the potential generalizability of our results to individuals with HIV in OAT. Studies have found status aware PLHIV are less likely to engage in high risk activities (Marks, Crepaz, Senterfitt, & Janssen, 2005) and access to OAT is associated with better retention (Strike, Millson, Hopkins, & Smith, 2013). Thus, there may be health behaviour and system differences between our cohort and other populations interested in HCV treatment initiation.

Additionally, we used OAT adherence with the assumption that it was necessary for DAA adherence (i.e. dropout from OAT would precipitate dropout from DAA). OAT retention is a strong predictor of long-term ART adherence among PWID (Roux et al., 2009), is associated with HCV treatment initiation (Midgard, Bramness, Skurtveit, Haukeland, & Dalgard, 2016), and has been found to improve adherence in studies conducted during the pegylatedinterferon era (Dimova, Zeremski, Jacobson, Hagan, & Des Jarlais, 2013). However, studies of people on OAT and recent injectors have found both populations able to complete a twelve week DAA treatment regimen irrespective of ongoing injecting drug use or OAT (Mason et al., 2017; Morris et al., 2017; Read et al., 2017), and studies which randomized people to immediate or delayed DAA treatment within OAT settings have observed loss to follow-up in the delayed treatment arms (Dore et al., 2016; Hilsden, Macphail, Grebely, Conway, & Lee, 2013). This suggests that ongoing injecting drug use is not associated with reduced response, prolonged delay in DAA initiation within OAT settings should be avoided, and although DAA retention and SVR are achievable outside OAT settings (Mason et al., 2017; Read et al., 2017), OAT remains an important setting for engaging PWID in HCV care and treatment. Given the cost of DAA, and concerns regarding treatment adherence and subsequent antiviral resistance, our study provides indirect evidence in support of further implementation science research for DAA treatment initiation time among PWID on OAT without incurring the costs of treatment or drop out.

The aim of this paper was to identify when OAT adherence sufficiently improved to inform DAA initiation in OAT settings. Using OAT adherence for HIV/HCV co-infected PWID, we found the likelihood of OAT adherence for a subsequent twelve weeks improves the longer the individual is undergoing treatment, and the more episodes of care the individual has had, unless the individual was ART adherent in which case HCV treatment can be initiated immediately. This evidence supports the need for further research into when treatment can

begin, and research showing OAT environments are useful points of care for initiating multiple therapies.

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Figure 1.
Conditional probability of being retained in OAT for additional 12 weeks by completed months on OAT, for first episode of OAT only.

Table 1

Summary statistics of all HIV/HCV co-infected PWID accessing OAT following HIV diagnosis in British Columbia, Canada: 1996 – 2013.

Cohort demographics ^a		n (%) N = 1427
Sex	Male	870 (61)
	Female	557 (39)
MSM	Yes	111 (8)
	No or unknown	1316 (92)
	Missing	595 (42)
	<200	254 (18)
CD4 count from within previous six months	200–349	211 (15)
	350–499	174 (12)
	500	193 (14)
Undetected pVL from within previous six months	Yes	166 (12)
	No	1261 (88)
OAT complies with BC OAT guidelines ^b	Yes	1114 (78)
	No	313 (22)
	Over a year	180 (13)
Previous OAT experience	31 days–1 year	185 (13)
	1–30 days	80 (6)
	No experience	982 (69)
OAT initiated in hospital	Yes	312 (22)
	No	1115 (78)
Dispensed medications for mental health in past year ^c	Yes	822 (58)
	No	605 (42)
Dispensed opiate agonists for pain management in past year ^d	Yes	333 (23)
	No	1094 (77)
	Contemporary	213 (15)
ART therapy type at OAT episode initiation	MDRT/traditional	184 (13)
	Not on therapy	1030 (72)
ART adherence 95% in 3 months prior to OAT episode initiation	Yes	167 (12)
	No	1260 (88)
Variable	n	Median (IQR)
Age at baseline	1427	37 (31–43)
Years since HIV diagnosis	1427	1 (0–4)
Chronic Disease Score	1427	3 (2–4)
Number of OAT episodes	1427	2 (1–4)
Total months of follow-up	4062	8 (2–18)
Proportion of months OAT compliant ^e	38,137	100 (25–100)
Proportion of months OAT adherent (95% treatments) ^e	38,137	44 (0–78)

^a Patient demographics at baseline of first episode of OAT following HIV diagnosis.

^b OAT titration or median effective dose (60 mg for methadone) during current month.

^c AHFS number: 281208, 281604, 281608, 282408, 282800.

^d AHFS number: 280808, 280812.

^e Number of months observed in dataset.

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Table 2

Proportion of all HIV/HCV co-infected PWID accessing first episode of OAT following HIV diagnosis retained for an additional 12 and 8 weeks from month on OAT.

Month on OAT	Number of individuals in OAT	12 weeks ^a n (%)	8 weeks n (%)
1st	1427	294 (20)	385 (27)
2nd	1160	274 (24)	366 (32)
3rd	1065	262 (25)	344 (32)
4th	995	275 (28)	350 (35)
5th	930	267 (29)	355 (38)
6th	883	270 (31)	341 (39)
7th	850	267 (31)	337 (40)

^aThe number of individuals retained for a subsequent 12 or 8 weeks may be higher than those reported in the preceding month because the number of individuals in OAT per month includes all members of our cohort with less than a month gap between treatment but the counts at 12 and 8 weeks include only those who are 100% OAT adherent for those subsequent durations.

Table 3

Multiple regression for odds of OAT adherence an additional 12 and 8 weeks from completed month on OAT.

	Additional 12 weeks		Additional 8 weeks
	Crude odds ratio	Adjusted odds ratio	Adjusted odds ratio
Time (reference = 1st month on OAT ^a)			
2nd month	1.11 (0.96, 1.28)	1.12 (0.97, 1.29)	1.15 (1.02, 1.31)
3rd month	1.13 (0.98, 1.31)	1.18 (1.02, 1.37)	1.23 (1.08, 1.40)
4th month	1.18 (1.02, 1.37)	1.21 (1.05, 1.41)	1.29 (1.13, 1.47)
5th month	1.13 (0.97, 1.31)	1.18 (1.01, 1.37)	1.28 (1.12, 1.46)
6th month	1.17 (1.00, 1.36)	1.21 (1.04, 1.41)	1.30 (1.13, 1.49)
7th month	1.25 (1.07, 1.45)	1.31 (1.13, 1.53)	1.35 (1.17, 1.55)
>7th month	1.41 (1.27, 1.57)	1.48 (1.32, 1.66)	1.60 (1.45, 1.77)
Female	0.65 (0.55, 0.77)	0.74 (0.63, 0.87)	0.77 (0.67, 0.88)
MSM	0.90 (0.64, 1.25)	0.88 (0.66, 1.29)	0.90 (0.70, 1.16)
Age (per 10 year increase)	1.53 (1.39, 1.68)	1.37 (1.26, 1.50)	1.33 (1.23, 1.43)
Chronic disease score	1.03 (1.01, 1.06)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
AIDS defining illness ever prior to treatment initiation	1.12 (0.92, 1.37)	1.00 (0.86, 1.16)	1.00 (0.88, 1.14)
CD4 cell count (reference = 500)			
Missing	1.00 (0.88, 1.12)	1.03 (0.91, 1.16)	0.96 (0.87, 1.07)
<200	0.97 (0.84, 1.12)	1.02 (0.89, 1.17)	0.95 (0.84, 1.08)
200–349	1.07 (0.94, 1.22)	1.09 (0.96, 1.23)	1.07 (0.96, 1.20)
350–499	1.09 (0.97, 1.23)	1.09 (0.97, 1.23)	1.09 (0.97, 1.21)
Previous OAT experience	1.65 (1.32, 2.09)	1.38 (1.17, 1.62)	1.31 (1.14, 1.51)
OAT complies with guidelines	1.72 (1.55, 1.91)	1.65 (1.49, 1.83)	1.55 (1.41, 1.70)
Initiation of OAT during hospitalization	1.19 (1.02, 1.39)	1.15 (0.99, 1.33)	1.15 (1.01, 1.30)
Cumulative OAT adherence >95%	2.11 (1.94, 2.30)	2.02 (1.86, 2.21)	2.30 (2.14, 2.49)
Medications for mental health in past year	1.35 (1.15, 1.58)	1.25 (1.07, 1.46)	1.21 (1.07, 1.38)
Opiate agonists for pain management in past year	1.03 (0.89, 1.20)	0.85 (0.74, 0.98)	0.87 (0.77, 0.98)
Changes in OAT prescriber during episode	1.15 (1.05, 1.26)	0.98 (0.89, 1.08)	0.98 (0.90, 1.07)

^aOAT = opioid agonist treatment.

Table 4

Multiple regression for odds of OAT adherence an additional 12 weeks from completed month on OAT - stratified by ART adherence at episode baseline.

	ART adherent ^a	Non ART-adherent ^b
Time (reference = 1st month on OAT)		
2nd month	1.12 (0.82, 1.51)	1.10 (0.94, 1.29)
3rd month	1.08 (0.79, 1.47)	1.19 (1.01, 1.40)
4th month	1.24 (0.91, 1.71)	1.17 (0.99, 1.39)
5th month	1.07 (0.77, 1.48)	1.17 (0.99, 1.39)
6th month	1.06 (0.76, 1.47)	1.21 (1.02, 1.44)
7th month	1.11 (0.80, 1.56)	1.33 (1.11, 1.58)
>7th month	1.17 (0.91, 1.49)	1.51 (1.32, 1.72)
Female	1.09 (0.76, 1.57)	0.68 (0.57, 0.81)
MSM	1.38 (0.79, 2.40)	0.72 (0.51, 1.01)
Age (per 10 year increase)	1.30 (1.08, 1.56)	1.36 (1.23, 1.50)
Chronic disease score	1.01 (0.97, 1.06)	1.01 (0.98, 1.03)
AIDS defining illness ever prior to treatment initiation	0.99 (0.74, 1.34)	0.96 (0.82, 1.13)
CD4 (reference = 500)		
Missing	1.28 (0.98, 1.67)	1.02 (0.89, 1.17)
<200	0.90 (0.66, 1.21)	1.05 (0.90, 1.24)
200–349	0.93 (0.72, 1.19)	1.13 (0.98, 1.31)
350–499	0.95 (0.76, 1.19)	1.14 (0.99, 1.31)
ART adherence ≥95% at current month	0.92 (0.76, 1.13)	1.15 (1.04, 1.26)
Previous OAT experience	1.04 (0.70, 1.55)	1.45 (1.22, 1.72)
OAT complies with guidelines	1.65 (1.32, 2.05)	1.66 (1.47, 1.87)
Initiation of OAT during hospitalization	1.55 (1.12, 2.15)	1.07 (0.91, 1.27)
Cumulative OAT adherence >95%	1.85 (1.52, 2.25)	2.09 (1.90, 2.31)
Medications for mental health in past year	0.84 (0.55, 1.27)	1.31 (1.10, 1.54)
Opiate agonists for pain management in past year	1.00 (0.71, 1.39)	0.83 (0.71, 0.97)
Changes in OAT prescriber during episode	1.04 (0.84, 1.30)	0.96 (0.86, 1.07)

^a ART adherent group (ART adherence ≥95% for three months prior to OAT initiation) is comprised of 790 episodes OAT capturing 7219 months of follow-up among 499 patients^c in the study.

^b ART non-adherent group (ART adherence <95% for three months prior to OAT initiation) is comprised of 3272 episodes of OAT capturing 29,035 months of follow-up among 1302 patients^c in the study. This group includes patients that have yet to initiate ART.

^c The number of patients in the adherent and non-adherent strata will not add up to the total number of patients captured in the cohort because patients can provide data on both strata by episode of care.