Title
Engagement in HIV care and viral suppression following changes in long-term opioid therapy for treatment for chronic pain

Author
Silvis, Janelle

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Engagement in HIV care and viral suppression following changes in long-term opioid therapy for treatment for chronic pain

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Janelle Silvis

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Approved:

DocuSigned by:
Heather Leutwyler
012039073579437...

Heather Leutwyler
Chair

DocuSigned by:

Phillip Coffin

DocuSigned by:
Natalie L. Wilson
64818D0FC430444...

Natalie Wilson

Committee Members

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ABSTRACT

Engagement in HIV care and viral suppression following changes in long-term opioid therapy for treatment for chronic pain

Janelle Silvis

Objectives: To determine associations between dose changes in opioids prescribed for chronic non-cancer pain and HIV care outcomes.

Methods: Using medical record data from January 1, 2012 to June 30, 2019 for 300 publicly insured HIV-positive primary care patients prescribed opioids for chronic non-cancer pain in San Francisco, we examined associations between opioid dose changes and both time to disengagement from HIV care and having a detectable viral load using logistic regression models. Models controlled for time-dependent confounding and informative censoring using inverse probability of treatment and retention weights, respectively.

Results: Discontinuation of prescribed opioids was associated with increased odds of disengagement in care at 3 months (OR: 2.21, 95% CI: 1.19-4.12), 6 months (3.66, 1.94-6.93) and 9 months (3.75, 1.76-7.97) after discontinuation. An increased opioid dose was associated with lower odds of having a detectable viral load (0.64, 0.43-0.95).

Conclusions: Discontinuation of opioids prescribed for chronic pain is associated with disengagement from HIV care.

Policy Implications: Providers and policy makers must consider the unintended consequences of opioid stewardship and its potential impacts on retention in care.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

HIV: Human Immunodeficiency Virus

PLWH: People living with HIV

MME: Milligram Morphine Equivalents

CDC: Centers for Disease Control and Prevention

IPW: Inverse probability weight

IPTW: inverse probability of treatment weight

IPRW: inverse probability of retention weight

ICD: International Classification of Disease

APN: Advanced Practice Nurse

INTRODUCTION

Of the 1.2 million adolescents and adults living with HIV in the United States, there were an estimated up to 90% living with chronic pain. [1,2] [3] Current HIV antiretroviral therapy regimens are effective in maintaining virologic suppression, improving quality of life, and reducing HIV-related morbidity and mortality.[4] Yet, as the population of people living with HIV (PLWH) age, they are faced with other comorbidities such as chronic pain.[5] Independent of HIV viral load, PLWH report muscular, joint, and neuropathic pain as some of the most bothersome and prevalent symptom burden.[6] Estimates of the prevalence of PLWH are also more likely than HIV uninfected patients to receive opioids[7] at higher doses for the treatment of pain[8] and use other illicit substances, which may increase the risk for opioid use disorder.[9] Since 2010, increasing efforts have been made to reduce reliance upon opioids for chronic pain, culminating in the Centers for Disease Control and Prevention (CDC) 2016 opioid prescribing guidelines.[10,11] Some strategies to reduce prescription opioid use include tapering long-term opioid doses to less than 90 morphine milligram equivalents (MME) daily, reviewing patient opioid history using state prescription drug monitoring programs, and urine drug testing.[10] These efforts have reduced the number and dose of opioid prescriptions in the United States;[12,13] however, pain and addiction experienced by patients remain insufficiently addressed.[14]

Untreated or undertreated chronic pain among PLWH has been associated with decreased antiretroviral adherence[15] and increased odds of no-show visits,[16] creating a potential conflict between HIV care outcomes and opioid stewardship. Moreover, patients who have experienced cessation of opioids for chronic pain have been shown to be at greater risk of depression, suicide, illicit opioid use, opioid-related emergency room admissions, and death from opioid overdose

than those who did not experience opioid cessation.[11,17-19] Some HIV providers have demonstrated selective compliance with opioid prescribing guidelines; which have potentially been attributed to goals of sustaining rapport with patients and keeping them connected to care, in addition to maintaining pain control.[20,21] In such studies, providers note that although opioids may generate use disorders and distract from other care goals, they may also reduce illicit opioid use, improve attendance at visits, and sustain engagement in care.[21] In a systematic review of 102 studies addressing opioid medications, chronic pain, and treatments agreements of urine drug testing; having chronic pain and no prescribed opioids was associated with virologic failure.[1] However, no study published to-date has reported the impact of reducing or stopping opioids on patient engagement among PLWH who were receiving long-term opioid therapy for chronic pain. Therefore, the purpose of this study was to examine the association of opioid dose reduction or cessation with disengagement in care with a direct effect on HIV viral load. We hypothesized that opioid cessation or dose reductions would be associated with increased odds of disengagement in care and detectable viral load.

METHODS

Using data from a retrospective cohort study of PLWH with chronic non-cancer pain, we modeled associations of opioid dose changes with 1) time to disengagement from HIV care using pooled logistic regression model, where each observation was measured as one patient-month; and 2) detectable HIV viral load using logistic regression, where each observation was the quantitative result of HIV-RNA test. This study was approved by the University of California San Francisco Institutional Review Board (#16-19352).

Study Sample

Patients were selected from 7 HIV primary care outpatient clinics serving only publicly insured or uninsured individuals in San Francisco. Inclusion criteria included: ≥ 18 years of age; having been prescribed opioids for chronic non-cancer pain for at least 3 months during the timeframe of January 1, 2013 to December 31, 2015; having an HIV diagnosis prior to December 31, 2015; and being alive through December 31, 2015. A total of 927 patients met the criteria and 300 patients were randomly selected for the analysis. Descriptive analysis was performed to describe patient demographics and sample characteristics.

Measures

Electronic health record data were manually and electronically extracted. Data electronically extracted included demographics, laboratory data (HIV viral load, CD4 count, urine drug screen results), and all ICD-10 codes for visit encounters during the study period (Appendix Table A). Data collected manually included details on opioid prescriptions (type, dose, dates of prescriptions), concerning behaviors documented by the provider (i.e. ongoing alcohol, cocaine, methamphetamine, or illicit opioid use; suspected diversion of opioids; early refills; reported lost opioid medications; opioid overdose), and emergency department visits by opioid-relatedness. Charts were reviewed by a physician to ensure accuracy using a previously published procedure.[19] Mortality data were collected from the California Electronic Death Record System.

Exposure

Opioid dose changes were defined using daily prescription data from medical charts and converted to daily MME using standard methods.[22,23] Dose changes were categorized as either

an increase or decrease (30% relative change from the last prescription prior to change in daily prescribed MME), a discontinuation of opioid MME (any change to zero MME), or no change in MME. Because a relative increase from zero MME is undefined, any dose increase from zero MME was also categorized as an increase. The 30% threshold aims to capture clinically meaningful dose changes and has been applied in other studies.[19] The direction and relative magnitude of dose changes were obtained by comparing a patient's pre-change MME and their MME 30 days after the dose change. The rationale for this decision was to reduce unexplained variability from short-term fluctuations in opioid dose, which were not relevant to our primary research questions.

Outcomes

Disengagement from HIV care was defined as having fewer than two viral load tests in 365 days. This definition aligns with the American Academy of HIV Medicine guidelines, which recommends at least two viral load tests per year.[24] The start of each patient's analysis period was defined as the earliest date on which they had at least two viral load tests within 365 days and at least 365 days of follow-up data. Given the recommendation of two viral load tests per year, patients receiving the standard of care would be expected to have one test every six months on average. Therefore, we defined the date of disengagement as 180 days after the patient's last viral load test before not having one for >365 days. The end of each patient's analysis period was defined as, the date on which they experienced the outcome (disengagement from care), moved away or to a different health system, death, or reached the end of study follow-up period; whichever occurred first. In our time-to-event setup, the disengagement outcome was dichotomized as a binary variable set to zero in the months before disengagement, one in the

month of disengagement for patients who experienced the outcome and missing in the months following disengagement or exit from the cohort. The unit of analysis was patient-months, with the analysis dataset including every patient-month during each patient's analysis period.

Detectable viral load was evaluated as a binary variable indicating the results of a viral load test, with detectable defined as >200 copies/mL. The start of each patient's analysis period was defined as the earliest date on which they had at least one viral load and 365 days of follow-up data. The end of the patient analysis was defined consistent with the disengagement model. The unit of analysis was the patient viral load test, with the analysis dataset including every viral load test occurring during each patient's analysis period. Additional details on analysis period rationale are available in the appendix of this article.

We assumed that dose changes could be associated with both outcomes for up to one year following the occurrence of the dose change. We also assumed that a dose change would not have any effect on a patient's viral load for at least 30 days, thus for the viral load analysis we defined dose changes as occurring 30 days after they actually occurred.

Covariates

Both analyses included several time-invariant and time-dependent covariates. We included covariates that were hypothesized to be related to both future dose changes and the outcomes that were obtainable from patient medical records. Due to clinical similarities between the two outcomes, each model included the same set of covariates. Time-invariant covariates included patient race/ethnicity, sex, and age at baseline. Time-dependent covariates included monthly

mean opioid dose; any concerning behaviors documented by a provider; any urine drug screening positive for cocaine, amphetamines, or heroin (6-MAM); detectable viral load (>200 copies/mL); CD4 count; and any substance use-related healthcare visit (see Appendix).

Inverse Probability of Treatment and Retention Weights

For both outcomes, we hypothesized that bidirectional effects linking opioid dose changes and other clinical covariates would introduce time-dependent confounding, which we accounted for using stabilized inverse probability of treatment weights (IPTWs).[25,26] Both models also accounted for differential loss to follow-up using stabilized inverse probability of retention weights (IPRWs).[25,26]

To calculate stabilized weights for each analysis, we constructed separate longitudinal datasets composed of patient-month observations spanning respective analysis periods. For the IPTWs, we estimated the probability of each type of dose change for each patient-month as a function of past dose change and covariates using multinomial logistic regression models with dose change as the multinomial outcome. For the IPRWs, we estimated the probability of being censored during each patient-month as a function of past treatment and covariates using a pooled logistic regression model with a binary outcome indicating each patient's last month of follow-up, then estimated IPRWs using the complement of the fitted probability of censoring. The final inverse probability weights (IPWs) were equal to the product of the stabilized IPTWs and IPRWs for each patient-month. Although weights for both analyses were calculated using the same underlying sample and clinical data, analysis periods differed for each and thus so did the final weight estimates (full details are available in Appendix).

Disengagement from Care Model

Dose changes were included in the model as separate indicator variables corresponding to increases, decreases, and discontinuations, with no change as the reference. Assuming that dose changes could influence the risk of a patient disengaging from care beyond the month in which the dose change occurred, we carried forward dose changes either until the patient's next dose change or for up to 12 months, whichever was sooner. After 12 months, patients were considered to have no dose change. We allowed for the effect of dose changes to vary over time by including a variable that captured the sequential count in months since a dose change occurred. These sequential count variables were first included as three-knot restricted cubic splines with knots at 3, 6, and 9 months following the dose change. If the spline terms were not statistically significant at $p<0.2$ as assessed using Wald tests, only a linear term was included; if the linear term was not significant at $p<0.2$, the linear term was also removed and the effect the dose change was modeled as constant. If a trend was indicated for a particular type of dose change, the coefficient for the corresponding indicator variable can be interpreted as the immediate effect of that type of dose change, whereas delayed effects can be calculated using linear combinations of the immediate effect and the change in effect over time. If no trend is indicated, the coefficient for the corresponding indicator variable estimates the constant effect.

Our final estimates were obtained by fitting a pooled logistic regression model to the analysis dataset of patient-months. Independent variables included the indicator and appropriate trend variables for each type of dose change, all baseline covariates (including baseline values of time-dependent covariates), and a four-knot restricted cubic spline for months since observations

began (December 31, 2012), with knots at the 5, 35, 65, and 95 percentile values. To adjust for time-dependent confounding and differential loss to follow-up, each patient-month was weighted by its corresponding stabilized IPWs. If a trend in the effects of dose change was indicated, we presented the immediate effect and the delayed effect after 1, 3, 6, and 9 months; otherwise, we present only a single constant effect. Confidence intervals (95%) were calculated using cluster robust standard errors to account for clustering by participant.

Viral Load Model

Because the unit of analysis was a patient viral load test, dose changes only needed to be defined for the period preceding each viral load test. Specifically, for each patient viral load test, dose change was defined as the most recent dose change up to 365 days prior to the viral load test. Dose changes and possible time-varying effects were operationalized as described for the disengagement from care analysis; however, the unit of time was days instead of months. Thus, time-varying effects were included as either linear or spline terms for days since the dose change, with spline knots at 90, 180, and 270 days. This model also controlled for secular trend using a four-knot restricted cubic spline in days since December 31, 2012 (with knots defined using quantiles).

Final estimates were obtained by fitting a logistic regression model to the dataset of viral load tests and the same independent variables as described for the disengagement analysis. To adjust for time-dependent confounding and differential loss to follow-up, each patient viral load observation was weighted by the IPW corresponding to months between cohort entry and the viral load assessment. Constant and time-varying dose change effects with 95% confidence

intervals and cluster robust standard errors are presented as described for the disengagement from care analysis.

Sensitivity Analyses

We conducted several sensitivity analyses described in detail in the appendix. For both outcomes, we conducted analyses using trimmed IPTWs as well as using IPTWs and IPRWs estimated under different covariate specifications (Appendix Table B & C). For the main disengagement from care analysis, we assumed patients disengaged from care exactly 180 days after the date of their last viral load test before they had a >365-day lapse between tests; we conducted a sensitivity analysis in which we randomly varied this date for each patient who experienced the outcome and characterized the resulting estimates over 1000 iterations (Appendix Table D). For the viral load analysis, we allowed dose changes to have an immediate effect as opposed to starting at least 30 days after the dose change occurred (Appendix Table B).

RESULTS

The 300 PLWH in our sample had a median age of 50 years; 73.7% were male; and 44.3% were Black, 43.0% White, and 10.7% Hispanic (Table 1). While all were prescribed opioids for at least 3 months between 2013 and 2015, the proportion receiving opioids varied by year, from a peak of 93.5% in 2014 to a nadir of 58% in 2019. Among those prescribed opioids in any given year, the mean dose ranged from 162-193 MME. In our sample, 66.3% experienced at least one dose increase, 47.7% experienced at least one opioid dose decrease, and 52.7% experienced at least one opioid discontinuations during the entire study period. Around half had at least one urine drug screen positive for cocaine, amphetamines, or heroin (48.3%); 57.7% had a

concerning behavior noted in the chart by a provider; and 57.0% had a substance use diagnosis, or an emergency department visit for over-sedation from opioids. About two-fifths (41.3%) had at least one episode of disengagement from care and 51.7% had at least one viral load > 200 copies/ml during the entire study period. Most demographic and clinical characteristics were similar by outcomes, although a larger proportion of White compared to Black patients experienced disengagement from care. A greater proportion of patients with detectable viral load had urine drug screens positive for cocaine, amphetamines, or heroin, and substance use ICD diagnostic codes or emergency department visits due to opioid oversedation (Tables 2 & 3).

Opioid dose and engagement in care

In our main analyses, controlling for both baseline and time-dependent confounding and differential loss to follow-up, and discontinuation of prescribed opioids, was associated with increased odds of disengagement from care 3 months (OR: 2.21 95% CI: 1.19-4.12), 6 months (OR: 3.66, 95% CI: 1.94-6.93) and 9 months (OR: 3.75, 95% CI: 1.76-7.97) following the discontinuation. Reductions or increases in opioid dose of 30% or more, were not associated with disengagement from care (Table 4). Results were largely consistent across sensitivity analyses (Appendix Table B).

Opioid dose and viral load

Experiencing a dose increase was associated with lower odds of having a detectable viral load (OR 0.64 [95% CI 0.43-0.95). However, these results were not statistically significant in sensitivity analyses (Appendix Table B-D). Discontinuations or reductions in opioid dose were not associated with having a detectable viral load (Table 4).

DISCUSSION

The purpose of our study was to examine the association of opioid dose reduction or cessation with disengagement in care with a direct effect on HIV viral load. We followed a diverse population of PLWH throughout a period of substantial changes in opioid prescribing policies and practices. Most patients underwent either a decrease or discontinuation of their opioid treatment during the study period. Discontinuation of prescribed opioids for chronic pain was associated with subsequent disengagement from HIV care, a significant concern for the health of PLWH.

Our findings of disengagement in care for PLWH highlight the importance of balancing opioid stewardship and retention in care. Implementation of opioid prescribing guidelines has been challenging for healthcare systems, clinicians, and patients.[27] For example, while the 2016 CDC guidelines recommended opioid doses not be raised above 90 MMEs per day, many healthcare systems interpreted this as meaning that all patients on higher doses should be lowered to below 90 MMEs – and that most patients should not be on opioids long-term at all for non-malignant pain. The CDC has since clarified that those guidelines were intended for opioid naïve persons, and were not meant to be applied to those already on high doses of opioids,[28] and the US Food and Drug Administration has warned against treating opioid-experienced patients the same as opioid-naïve patients.[29] In those who use opioids for chronic pain treatment, abrupt opioid cession increases the risk of illicit opioid use and opioid overdose death.[16,17] To achieve both patient retention and opioid stewardship in this population, novel and patient-centered opioid management strategies should be evaluated. An increasing body of scientific literature supports

patient-centered opioid management plans,[30] which include building a strong relationship with patients prior to attempting an opioid taper, giving patients the choice to select which medications might be tapered and at what rate, and ensuring low-barrier access to medications such as buprenorphine to treat opioid use disorder.[31,32] The use of buprenorphine for opioid use disorder reduces use of opioids and risk of opioid overdose. [33]

The relationship between opioid prescribing on viral load and engagement in care is complex. Research into the HIV care continuum[4] finds that engagement in care is essential for viral suppression,[4] and that disengagement has been associated with both increased viral load and mortality.[34] We found an association between pain management with an increase in opioid dose to pain control, and maintaining viral load suppression; suggesting that patients stayed engaged in their HIV care when their dose was increased, but did not find an association between opioid dose reductions or discontinuations, and viral load. It is possible that our study did not detect such an association because patients who had disengaged from care and may have been more likely to have a detectable viral load, could not be identified. We controlled for this possibility of informative censoring using inverse probability of retention weight. Although we observed a rich set of clinical covariates, it remains possible that we could not account for all relevant differences between patients who were censored and those who remained under follow-up.

These results also may be relevant for patients with other complex chronic diseases. For example, untreated chronic pain has been associated with increased hemoglobin A1c levels in patients with diabetes mellitus.[35] Diabetes care is similar to HIV treatment, in that engagement and medication adherence are critical to successful management. If an association between

discontinuation of opioids and care outcomes were present among those with diabetes or other chronic diseases, that would provide further evidence of the urgent need for more sophisticated approaches to opioid stewardship across clinical care.

Our study has several strengths. We were able to obtain a robust sample of patients who are demographically diverse. The sample was chosen randomly to ensure they are representative of PLWH. The data set included multiple years of data to analyze and follow patient outcomes. Lastly, we were able to capture significant opioid dose reductions in our sample over time that are reflective of national prescription opioid dose trends.

Our study has limitations. First, all data were from patient medical records, which are not subject to systematic protocols and thus documentation of clinical characteristics and events may vary across both patients and providers. Our data set did not include other potential covariates such as income, housing status, or mental health comorbidities, which may impact outcomes of engagement in care and viral suppression. Second, our analyses were observational in nature and thus vulnerable to a wide variety of biases. However, under assumptions of correct model specification, no unmeasured confounding, and censoring that is noninformative conditional on covariates, our estimates can be interpreted as causal effects of opioid dose changes on each of our outcomes. Additionally, our model looked only at 30% reduction or increases of total MMEs and results may be different if a higher or lower percentage threshold was used. Lastly, our sample consisted of patients in safety net primary care clinics, with high rates of substance use, and may not be generalizable to other patient populations or geographical regions.

PUBLIC HEALTH IMPLICATIONS

Discontinuation of opioids prescribed for chronic pain was associated with disengagement from HIV care. These results add to the growing evidence base of harms associated with shifting opioid prescribing policies and practices. While limiting opioid prescribing is necessary, it is critical to identify way to simultaneously retain patients in care and protect the most vulnerable from untoward clinical outcomes.

NURSING IMPLICATIONS

The findings of this research highlight the unintended consequences of opioid stewardship practices, specifically their effect on engagement in life-saving HIV care. Registered nurses and advanced practice nurses (APNs) are often at the forefront of assessing and managing chronic pain. Nurses are well positioned to lead efforts to retain patients in care and practice in such a way that does not focus on opioid prescribing exclusively. The nursing approach can be utilized to wholistically take into account factors that may lead to poorly managed chronic pain, risk factors leading to opioid use disorder, and other detrimental health outcomes.

Nurses are often responsible for completing basic pain assessments, administering analgesia as prescribed, ensuring access to other forms pain management, providing patient education, and coordinating care with a multidisciplinary pain management team[35]. In addition to managing acute and chronic pain, APNs have the ability to assess psychosocial impacts on pain, lead efforts to provide alternative pain management strategies in clinic, and address substance use disorders in the inpatient and outpatient setting, such as providing access to buprenorphine[35, 36]. Furthermore, APNs can lead medication follow-up clinics[33]. Lastly, nurses have always held a

unique role in providing an informal link between non-engaged patients and the services in place to support them[34]. Nurses are able to develop a unique trust with patients by providing non-discriminatory health care and serve as a link between vulnerable communities and the greater health care systems, policies, and health care stake holders[36]. For example, in the context of HIV care, evidence shows that nurses play a pivotal role in antiretroviral treatment in PLWH by building therapeutic relationships, teaching and sharing knowledge, coordinating care, considering the social conditions that may interfere with antiretroviral adherence, and connecting patients to resources and referrals to social services.[38] The findings of this research suggest an important role for both RNs and APNs in pain management, care engagement, and chronic disease management.

TABLES

Table 1: Participant demographics and longitudinal measures (n=300)

Characteristic/Measure	**n**	**(%)**
Demographic Characteristics		
Total Number of Patients	300	
Age at baseline, *median (IQR)*	50	(45-56)
Race/Ethnicity		
Non-Hispanic Black	133	(44.3)
Non-Hispanic White	129	(43)
Hispanic	32	(10.7)
Non-Hispanic other/mixed race	6	(2)
Gender		
Male	221	(73.7)
Female	79	(6.3)
Longitudinal Measures*		
Number of months of follow-up, *median (IQR)*	61	(34-76)
Mean opioid dose among patients prescribed opioids by year, *mean (SD)*†		
2013 (n = 254; # prescribed any opioids during year = 232 [91.3%])	193	(336.2)
2014 (n = 262; # prescribed any opioids during year = 245 [93.5%])	171	(312)
2015 (n = 258; # prescribed any opioids during year = 238 [92.2%])	162	(312)
2016 (n = 233; # prescribed any opioids during year = 188 [80.7%])	174	(296.8)
2017 (n = 215; # prescribed any opioids during year = 164 [76.3%])	167	(290.8)
2018 (n = 178; # prescribed any opioids during year = 118 [66.3%])	173	(310.6)
2019 (n = 138; # prescribed any opioids during year = 80 [58.0%])	168	(285.8)
Experienced ≥ 1 opioid dose increase	199	(66.3)
Experienced ≥ 1 opioid dose decrease	143	(47.7)
Experienced ≥ 1 opioid dose discontinuation	158	(52.7)
Disengaged from care	124	(41.3)
Concerning behavior documented by provider	173	(57.7)
Positive urine drug screen for cocaine, amphetamines, or heroin	145	(48.3)
Diagnosis related to illicit substance use or ≥ 1 opioid oversedation emergency department visit	171	(57)
Detectable viral load during follow-up	155	(51.7)
CD4 count, *mean (SD)*‡	555	(301)

IQR = interquartile range; SD = standard deviation

*Longitudinal measures correspond to the analysis period for the disengagement from care analysis, which is distinct from the analysis period for the detectable viral load analysis.

†Mean opioid dose by year is calculated as the mean of patients' mean daily dose in each year, including only days when patients were prescribed opioids.

‡Mean CD4 count is calculated as the mean of patients' mean CD4 count among all their CD4 tests.

Table 2: Participant demographics among patients (n=300) and longitudinal measures among patient-months (n=16309) by disengagement from care status

	All Patients		Patients Who Did Not Disengage from Care		Patients Who Disengaged from Care	
Characteristic/Measure	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Demographic Characteristics						
Total Number of Patients	300	(100)	176	(58.7)	124	(42.3)
Age at baseline, *median (IQR)*	50	(45-56)	50	(45-57)	49.5	(45-56)
Race/Ethnicity						
Non-Hispanic black	133	(44.3)	84	(47.7)	49	(39.5)
Non-Hispanic white	129	(43)	70	(39.8)	59	(47.6)
Hispanic	32	(10.7)	17	(9.7)	15	(12.1)
Non-Hispanic other/mixed race	6	(2)	5	(2.8)	1	(0.8)
Gender						
Male	221	(73.7)	133	(75.6)	88	(71)
Female	79	(26.3)	43	(24.4)	36	(29)
Longitudinal Measures [a]	**All Patient-Months**		**Patient Months Without Disengagement from Care**		**Patient-Months With Disengagement from Care**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Total Number of Patient Months	16309	(100)	16185	(99.2)	124	(0.7)
Most recent dose change within past year						
No change	9959	(61.1)	9889	(61.1)	70	(56.5)
Increase	2811	(17.2)	2796	(17.3)	15	(12.1)
Decrease	1540	(9.4)	1533	(9.5)	7	(5.6)
Discontinuation	1999	(12.3)	1967	(12.2)	32	(25.8)

Characteristic/Measure	All Patients		Patients Who Did Not Disengage from Care		Patients Who Disengaged from Care	
	n	(%)	n	(%)	n	(%)
Mean MME in past month, *mean (SD)*	139.9	(294.9)	140.1	(295)	111.2	(285.2)
Occurrence in past six months						
Concerning behavior documented by provider	2534	(15.5)	2515	(15.5)	19	(15.3)
Positive urine toxicology for cocaine, amphetamines, or heroin	2909	(7.8)	2891	(17.9)	18	(14.5)
Diagnosis related to illicit substance use or ≥ 1 opioid oversedation emergency department visit	4535	(27.8)	4496	(27.8)	39	(31.5)
Detectable viral load in most recent test	2601	(15.9)	2577	(15.9)	24	(19.4)
Most recent CD4 count, *mean (SD)*	573.3	(343.7)	572.8	(343.8)	632.5	(323.8)

IQR = interquartile range; SD = standard deviation; 6-MAM = 6-monoacetylmorphine

[a] Longitudinal measures correspond to the analysis period for the disengagement from care analysis, which is distinct from the analysis period for the detectable viral load analysis.

Table 3: Summary of measures preceding viral load tests included in detecting viral load analysis (n=4325 viral load tests among 300 patients)

	All Viral Load Tests		Undetectable Viral Load		Detectable Viral Load	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Number of viral load tests	4325	(100)	3348	(77.4)	977	(22.6)
Most recent dose change within past year [a]						
No change	2752	(63.6)	2155	(64.4)	597	(61.1)
Increase	707	(16.3)	572	(17.1)	135	(13.8)
Decrease	387	(8.9)	275	(8.2)	112	(11.5)
Discontinuation	479	(11.1)	346	(10.3)	133	(13.6)
Mean MME in past month, *mean (SD)*	131.6	(292.6)	141.3	(300.8)	98.4	(259.9)
Occurrence in past six months						
Concerning behavior documented by provider	742	(17.2)	521	(15.6)	221	(22.6)
Positive urine toxicology for cocaine, amphetamines, or heroin	883	(20.4)	580	(17.3)	303	(31)
Diagnosis related to illicit substance use or ≥ 1 opioid oversedation emergency department visit	1379	(31.9)	918	(27.4)	461	(47.2)
Detectable viral load in most recent test	950	(22)	322	(9.6)	628	(64.3)
Most recent CD4 count, *mean (SD)*	523.9	(336.9)	578.3	(334.5)	337.7	(272.4)

[a] As in our main detectable viral load analysis, dose changes are not considered to take effect until 30 days after the date of the dose change, thus most recent dose change indicates occurrence of a dose change at least 30 days prior to the date of the viral load test.

Table 4: Associations between opioid dose changes and time to disengagement from care and having a detectable viral load.

	Immediate Effect	Effect After 1 Month	Effect After 3 Months	Effect After 6 Months
Dose Change	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
No Change	Reference	Reference	Reference	Reference
Time to Disengagement in Care [a]				
Increase	1.1 (0.60-2.00)	No Trend Indicated (p > 0.2)		
Decrease	0.32 (0.03-4.17)	0.45 (0.06-3.13)	0.86 (0.34-2.18)	1.43 (0.39-5.23)
Discontinuation	1.18 (0.44-3.21)	1.46 (0.63-3.37)	2.21 (1.19-4.12)	3.66 (1.94-6.93)
Detectable Viral Load [b]				
Increase	0.64 (0.43-0.95)	No Trend Indicated (p > 0.2)		
Decrease	1.27 (0.79-2.03)	No Trend Indicated (p > 0.2)		
Discontinuation	0.89 (0.58-1.38)	No Trend Indicated (p > 0.2)		

[a] Estimated using logistic regression models controlling for baseline covariates and controlling for time-dependent covariates and differential loss to follow-up using inverse probability of treatment and retention weights.

[b] Estimated using logistic regression models controlling for baseline covariates and controlling for time-dependent covariates and differential loss to follow-up using inverse probability of treatment and retention weights, with 30-day delayed effect for opioid dose changes.

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