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Drug and Alcohol Dependence

Opioid use trajectory groups and changes in a physical health biomarker among HIV-positive and uninfected patients receiving opioid agonist treatment

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ABSTRACT

Background: Objective outcomes for measuring the physical health effects of substance use disorder treatment are needed. We compared the responsiveness of CD4, HIV-1 RNA and a biomarker index (VACS Index 2.0) to changes in opioid use among people with HIV (PWH) and uninfected individuals receiving opioid agonist treatment (OAT).

Methods: Electronic health record data were used to identify patients who received ≥90 days of OAT and had ≥1 urine toxicology test in the Veterans Aging Cohort Study. Trajectory models identified patterns of opioid urine toxicology results. We used linear regression adjusted for age and race/ethnicity to determine associations between opioid toxicology groups and biomarker changes from up to one-year pre OAT to 3–15 months after OAT initiation.

Results: Among 266 with detectable HIV-1 RNA, 366 with suppressed HIV-1 RNA, and 1183 uninfected patients, we identified five opioid toxicology groups ranging from consistently negative (54%) to consistently positive (9%). Among PWH with detectable HIV-1 RNA, all three biomarkers improved more for those consistently negative compared to those consistently positive (all p < .05). Among PWH with suppressed HIV-1 RNA, CD4 improved for those consistently negative; and worsened for those in the slow decrease toward negative group (p = .04). Among those uninfected, VACS Index 2.0 did not differ by opioid toxicology groups.

Conclusions: Among patients on OAT, changes in biomarkers are associated with opioid toxicology groups among PWH, but vary by HIV-1 RNA. These findings may be useful for measuring the health effects of OAT.

1. Introduction

The varied physiologic and health effects of drug use include direct toxicities from drugs and contaminants and indirect effects from infectious agents, non-adherence to medical regimens, poor nutrition, and impaired self-care (Al-Rabadi et al., 2018; Haber and Freyer, 2018; Haber and Gounder, 2018; Katz and Mazer, 2009; Malabanan and Jack, 2018; Sacerdote, 2006, 2008; Saitz, 2018; Sulis and Kimmel, 2018). A challenge in the field of addiction, that extends to the realm of Food and Drug Administration medication approval, is the lack of a comprehensive and objective outcome with which to measure these health effects and assess the benefits of substance use disorder treatment (Donovan

et al., 2012; Winchell et al., 2012). For instance, certain medication and pharmacologic treatments for substance use disorders may result in physical health benefits short of complete abstinence (Falk et al., 2010; Volkow et al., 2018). Given a need to identify health outcomes in patients receiving substance use treatments, the National Institute of Drug Abuse has funded research to identify health outcomes associated with changes in use of illicit drugs (https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-13-007.html). Measures such as self-report or urine toxicology may not always reflect harm due to drug use because individual patient susceptibility depends upon pre-existing physical vulnerability (Justice et al., 2016). This is particularly true among individuals with pre-existing organ system injury such as those with HIV infection or

other chronic health conditions (viral hepatitis, cirrhosis, anemia, or kidney disease) (Al-Rabadi et al., 2018; Haber and Freyer, 2018; Saitz, 2018; Sulis and Kimmel, 2018).

Medical comorbidities, such as hepatitis C, HIV and certain infectious diseases are common among those with opioid use disorder, especially people who inject drugs (PWID) (Page et al., 2018; Sulis and Kimmel, 2018; Tsui et al., 2014; Van Handel et al., 2016). Untreated substance use disorders are associated with poor HIV outcomes (Chitsaz et al., 2013; Hagan et al., 2008; Lima et al., 2014; Oldfield et al., 2019). Opioid agonist treatment (OAT) in persons with HIV (PWH) is associated with improved HIV disease management and other outcomes (Altice et al., 2011; Fiellin et al., 2011; Roux et al., 2009). The benefits of substance use disorder treatment in PWH historically extended to improvements in immune markers. Recent studies in PWH, however, have had difficulty discerning immunologic benefit from OAT using CD4 count and HIV-1 RNA viral load (Altice et al., 2011; Berg et al., 2011; Cooperman et al., 2012; Lucas et al., 2010). This finding likely reflects the benefit of current antiretroviral therapy (ART) despite ongoing drug use. Therefore, more expanded measures of health, that reflect immune system and other organ systems (e.g. liver, hematologic, kidney), may better capture health benefits of substance use disorder treatment among PWH rather than a sole focus on complete abstinence, CD4 count and HIV-1 RNA viral load.

The Veterans Aging Cohort (VACS) Index was developed to integrate HIV and commonly available 'non-HIV' biomarkers to improve differentiation of mortality risk among individuals receiving ART (Justice et al., 2010), and has been shown to substantially increase prognostic accuracy of estimates of mortality and overall health in PWH over traditional biomarkers alone (Justice et al., 2013; Tate et al., 2013). The VACS Index provides superior predictions for hospitalization and intensive care unit admission and is correlated with ART adherence, functional status, risk of fractures, health related quality of life, and level of inflammatory markers and both cardiovascular and HIV-related mortality compared to a "Restricted Index" comprised only of age, CD4, and HIV-1 RNA (Akgun et al., 2013a,b, 2014; Edelman et al., 2012; Erlandson et al., 2012; Justice et al., 2012a, b; Justice et al., 2013; Tate and Justice, 2010; Womack et al., 2011, 2013). The VACS Index is also associated with neurocognitive functioning (Marquine et al., 2014, 2016).

The original VACS Index was comprised of ordinalized measures of age, CD4, HIV-1 RNA, liver injury (FIB-4, derived from measures of platelets, aspartate aminotransferase, and alanine aminotransferase), hepatitis C virus (HCV) serology, hemoglobin, and a measure of kidney function (estimated Glomerular Filtration Rate, eGFR). The more recently developed VACS Index 2.0 converted these measures to continuous and incorporates continuous functional forms of albumin, white blood count, and body mass index (BMI) and provides improved discrimination over the original VACS Index (Tate et al., 2019). An advantage of the VACS Index over individual laboratory values is that it provides a mechanism to correlate health status change with mortality benefits. For instance, a 5 point increment in the VACS Index 2.0 is associated with a 30% increased risk of 5 year mortality – Hazard Ratio = 1.31 (1.30–1.31) over five years (Tate et al., 2017).

The purpose of the current study was to compare responsiveness of biomarkers to reductions in opioid use among those receiving OAT by identifying longitudinal opioid use change patterns using group-based trajectory modeling and then determining whether individual level changes in biomarkers are associated with opioid trajectory group membership among PWH (with and without HIV-1 RNA suppression) and among those uninfected. Specifically, we hypothesized that CD4, HIV-1 RNA, and the VACS Index 2.0 would improve in response to a reduction in opioid use among PWH with both detectable and suppressed HIV-1 RNA and that the VACS Index 2.0 would also improve in response to a reduction in opioid use among uninfected individuals.

2. Methods

2.1. Study design and setting

We used data from VACS, a large electronic medical record based cohort study of PWH and uninfected patients receiving care in the Veterans Health Administration (VA) that has been described in detail previously (Fultz et al., 2006; Justice et al., 2006). Demographic data, medical diagnoses (based on International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes), receipt of OAT, laboratory results (including urine toxicology analyses) and pharmacy records are extracted from electronic medical records via the VA Corporate Data Warehouse (CDW). The VACS study is approved by the Human Investigations Committee at Yale University and the VA Connecticut Healthcare System and is granted a waiver of informed consent.

2.2. Participants

We identified 1964 PWH and 3005 uninfected participants who received OAT (methadone or buprenorphine) for opioid use disorder between January 2000 and July 2015. Participants who were dispensed methadone from the VA opioid treatment programs were identified using VA stop code 523. Those who received sublingual buprenorphine or buprenorphine/naloxone formulations were identified using VA pharmacy data. We did not include patients who received methadone for treatment of pain. Of those receiving OAT, 868 PWH and 1274 uninfected patients received at least 90 days of OAT from January 2000 to July 2015; and 847 (98%) PWH and 1183 (93%) uninfected patients had at least one urine toxicology test during OAT. Of the 847 PWH, 660 (78%) had an HIV-1 RNA viral load value within the one year window prior to start of OAT. Of those 660, 570 (86%) had pre and post VACS Index 2.0 values and 613 (93%) had pre and post CD4 and viral load values, and were included in the analytic sample.

2.3. Data and definitions

Age in years was as of first OAT. Gender and race/ethnicity were determined from documentation in the electronic medical record. HCV infection status was based on detectable plasma HCV-RNA, positive antibody test, or documented ICD-9 diagnosis (Tate et al., 2019). Smoking status is assessed annually on all VA patients using a clinical reminder process and documented in the electronic medical record. Based on our prior work, we categorized patients into never, past, and current smoking categories consistent with their modal response over time (McGinnis et al., 2011). Alcohol-related diagnosis was based on ICD-9 codes.

Urine toxicology tests for opioids and other substances were administered throughout OAT treatment. Results for opioids were available as a dichotomous measure (positive/negative). We included tests obtained during treatment up to one year after treatment initiation.

Laboratory components necessary to calculate VACS Index 2.0 include platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), HCV serology, hemoglobin, eGFR, albumin, white blood count, CD4, HIV-1 RNA, and BMI. To calculate VACS Index 2.0 in uninfected individuals we assumed that CD4 count $\geq$ 500 cells/μL and HIV-1 RNA viral load < 20 copies/ml (Akgun et al., 2013a,b; Tate et al., 2014).

Changes in CD4, log HIV-1 RNA, and VACS Index 2.0 were calculated using corresponding values closest to and within 1 year prior to OAT (baseline) and the corresponding value 3 to 15 months after start of OAT choosing the most recent value available while on OAT. Changes were calculated by subtracting the pre-OAT value from the post-OAT initiation value so that positive values indicate an increase from pre to post OAT initiation; 0 indicates no change; and negative values indicate a decrease in values. Because changes in lab values are

often associated with the amount of time between measures, we annualized by dividing these change values by number of days between measures and then multiplied by 365 so that change is estimated over a one year period for use in statistical models. CD4, log HIV-1 RNA, and VACS Index 2.0 change variables were approximately normally distributed.

2.4. Statistical analysis

Longitudinal patterns of opioid use as indicated by urine toxicology test results during treatment were analyzed using group-based trajectory modeling (Nagin and Odgers, 2010) to identify distinctive patterns of urine opioid toxicology test results over time. As previously reported, trajectory modeling sorts each participant's measurements (opioid toxicology test results) into "clusters" and estimates distinct trajectories (Marshall et al., 2017). The procedure calculates each individuals' probability of belonging to each trajectory and assigns the individual to the trajectory with the highest probability of membership. We used number of days between start of OAT and each opioid toxicology test date within the twelve months after start of treatment as the time scale. We used a logit model (Jones and Nagin, 2012) and evaluated 3, 4, and 5 trajectory group models.

To better understand the analytic sample and generalizability of the results, we compared demographics and characteristics between those included and not included in the analytic sample (with and without a pre and post VACS Index 2.0 Score). Demographic and clinical characteristics were compared by HIV status and by opioid toxicology trajectory groups using chi-square tests to compare categorical variables, t-tests and one-way analysis of variance to compare approximately normally distributed variables, and Mann-Whitney rank sum and Kruskall-Wallis tests to compare nonparametric variables.

We determined associations between opioid toxicology trajectory groups and outcomes (change in CD4, change in log HIV-1 RNA, and change in VACS Index 2.0), using linear regression models. We treated opioid toxicology trajectory group as a categorical variable with consistently negative opioid toxicology as the referent group. Models were run with and without adjustment for age, and race/ethnicity. Gender was not included in models because there are few women in VACS which results in small cell sizes. Models of change in CD4 and log HIV-1 RNA were stratified by HIV-1 RNA status (detectable vs. suppressed HIV-1 RNA), and models of change in VACS Index 2.0 were stratified by HIV and HIV-1 RNA status. Because of concern that year (due to improvements in the efficacy of ART regimens), treatment type (methadone vs. buprenorphine), and/or baseline value of the corresponding outcome variable could moderate the association between opioid toxicology trajectory groups and the three outcomes, we tested for statistically significant interactions of opioid toxicology trajectory group with 1) treatment year, 2) treatment type, or 3) baseline value for the corresponding outcome dichotomized at mean value (for example for the change in VACS Index 2.0 models, we tested for a statistically significant interaction of opioid toxicology trajectory group and baseline VACS Index 2.0 dichotomized at mean value).

We ran several sensitivity analyses. The main models were rerun but without normalizing the change variables to reflect change over one year. We ran the models restricted to those with HCV as most of the sample is HCV positive. We evaluated adding treatment type, treatment year, and baseline value for the corresponding outcome as covariates in the main model to examine whether associations between urine toxicology results and outcomes would be attenuated with their inclusion. Treatment type (methadone or buprenorphine) and treatment year were important to include because in addition to improved effectiveness of HIV medications, prescribing of buprenorphine has increased over time. Lastly, because 5% of the urine toxicology values occurred after the post biomarker value (but still during OAT, within one year after OAT initiation, and no more than 14 days after the post biomarker), we created a urine toxicology trajectory variable excluding

those 5% and reran the main analyses. All statistical analyses were performed using Stata 14.0 (StataCorp LP, College Station, Tx).

3. Results

3.1. Demographics and characteristics

To better understand the analytic sample, we compared those with and without a pre and post VACS Index 2.0 Score. For both PWH and those uninfected, gender, smoking and HCV status were similar, and having consistently positive urine toxicology differed (9% vs. 16%) between those with and without both pre and post VACS Index 2.0 scores. Among PWH, compared to those with a pre and post VACS Index 2.0 value, those without were more liklely to have an alcohol related diagnosis (45% vs. 27%) and less likely to be on ARVs prior to start of OAT (21% vs. 59%). Among those uninfected, those without a VACS Index 2.0 score pre and post were slightly younger (mean age 51 years vs. 53 years) and more likely to be African American (70% vs. 61%) compared to those with a VACS Index 2.0 pre and post.

Of the PWH in the analytic sample, 266 had detectable HIV-1 RNA and 366 had suppressed HIV-1 RNA at baseline. The mean age was 53 years and ranged from 23 to 76 years. Most patients were male (99%), black (64%), had evidence of prior HCV infection (76%), and were currently smoking (88%) (Table 1). Of those treated with methadone (72%), 53% received treatment for at least a year and provided a median of 27 opioid toxicology tests. Of those treated with buprenorphine (27%), 52% recieved treatment for at least a year and provided a median of 14 opioid toxicology tests. Median time between the two VACS Index 2.0 Scores was 441 days (IQR = 379–473).

3.2. Opioid toxicology trajectory groups

Using all (positive/negative) opioid toxicology tests available during treatment as described above, we identified 5 trajectory groups representing levels of opioid use (Fig. 1). Model fit, as measured by Bayesian information criterion (BIC), improved substantially when increased from 4 to 5 groups and the smallest group in the 5-group trajectory contains 10% of the sample. The groups reflect the following patterns and are listed in order of the mean proportion of positive opioid toxicology tests within each group: 53% tested consistently negative, 15% rapidly decreased toward negative, 12% slowly increased toward positive, 10% slowly decreased toward negative, and 10% were consistently positive. Opioid toxicology trajectory group membership did not vary by HIV status or detectable/suppressed HIV-1 RNA among PWH. The mean percentages of positive opioid toxicology tests in each trajectory group in the analytic sample were 2% in those consistently negative, 19% in the rapid decrease toward negative group, 33% of those with a slow increase toward positive, 50% of those with a slow decrease toward negative, and 90% of those consistently positive.

Age, gender, smoking status, having an alcohol related diagnosis, and baseline HIV-1 RNA suppression and CD4 were similar by opioid toxicology trajectory groups (Table 2). Those in the consistently negative group were less likely to be African-American or receiving methadone compared to the other opioid toxicology trajectory groups. The consistently positive and consistently negative groups had a lower percent with HCV infection, compared to those in the other trajectory groups. Those who were consistently positive or slowly decreased toward negative had a higher mean percent of positive toxicology tests for marijuana and cocaine compared to those in the other opioid trajectory groups. Of the PWH, the percent on ART at baseline was similar between trajectory groups. Of the PWH not on ART at baseline, those in the consistently positive group were less likely to start ART (32%) within a year of starting OAT compared to the other groups (60% of consistently negative), but the difference was not statistically significant (p = .08).

Table 1
Characteristics of Patients at First Opioid Treatment from 2000 to 2015.

|	PWH Detectable HIV-1 RNA (n = 266)	PWH Suppresed HIV-1 RNA (n = 366)	Uninfected (n = 1183)	P-Value
Mean Age (SD)	51.9 (6.3)	55.1 (6.9)	53.1 (7.6)	< .001
Male (%)	99	99	99	.5
Race/Ethnicity (%)				.6
African-American	63	63	63	
Hispanic/Other	13	12	13	
White	24	25	24	
Year < 2010 (%)	85	56	56	< .001
Year ≥ 2010 (%)	15	44	44	
HCV Antibody Positive (%)	91	89	69	< .001
Smoking Status (%)				.04
Never	7	7	7	
Past	3	8	5	
Current	91	85	88	
Alcohol Related Diagnosis (%)	30	28	34	.031
Median # Treatment Episodes (IQR)	1 (1–2)	1 (1-2)	1 (1-2)	.02
Type of Treatment Initiated (%)				.005
Methadone	82	71	71	
Buprenorphine	18	28	28	
Both	0	1	1	
Median Days on Treatment (IQR)	584 (262–1264)	545 (253–1155)	568 (253–1199)	.8
Median Number of Opioid Toxicology tests (IQR)	24 (12–42)	22 (12–40)	21 (12–39)	.8
Median Days between first and last opioid toxicology tests (IQR)	319 (211–351)	332 (204–354)	329 (203–353)	.5
Opioid Toxicology Trajectory Groups (%)				.6
Consistently negative	50	53	55	
Rapid decrease toward negative	15	17	15	
Slow increase toward positive	15	11	11	
Slow decrease toward negative	11	10	10	
Consistently positive	9	8	10	
Median Proportion positive Opioid Toxicology (IQR)	0.09 (0-0.37)	0.08 (0-0.30)	0.08 (0-0.31)	.6
Mean VACS Index 2.0 Score (SD)	76 (16)	61 (15)	40 (12)	< .001
Mean Change in VACS Index 2.0 Score (SD)	−1.5 (13)	1.9 (12)	0.9 (7)	.004
On ART at baseline (%)	45	69	N/A	< .001
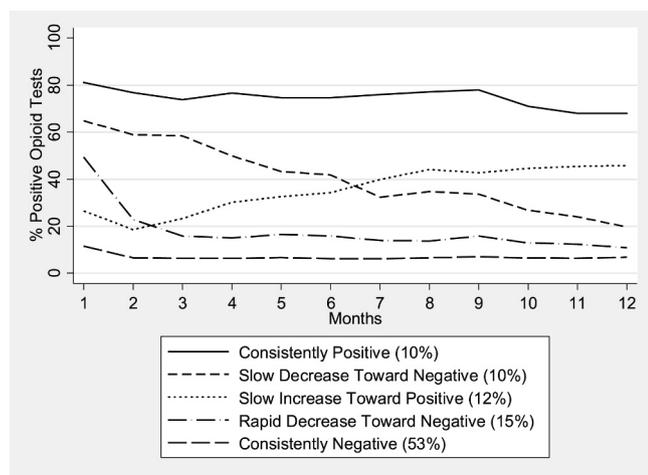
Fig. 1. Observed Percent Positive Opioid Toxicology Tests by Number of Months after Start of OAT, by Trajectory Groups.

3.3. Change in biomarkers among PWH with detectable HIV-1 RNA

Among PWH with detectable HIV-1 RNA, changes in CD4, HIV-1 RNA, and VACS Index 2.0 were statistically significantly associated with opioid toxicology trajectory groups in univariate analyses (Fig. 2). CD4 improved among those with consistently negative opioid toxicology by a mean of ~28 cells per mm^3 and worsened by a mean of ~34 cells per mm^3 for those with consistently positive opioid toxicology (Fig. 2). Change in CD4 differed between those with consistently positive opioid toxicology and those with consistently negative opioid toxicology in both univariate (p = .05) and adjusted (p = .04)

models. Log HIV-1 RNA improved among those with consistently negative opioid toxicology by around 1.1 and improved by a lesser amount (~0.6) for those with consistently positive opioid toxicology (Fig. 2). Change in log HIV-1 RNA differed between those with consistently positive opioid toxicology and those with consistently negative opioid toxicology in both the univariate analyses (p = .04) and in the adjusted models (p = .05) (Table 3). VACS Index 2.0 improved among those with consistently negative opioid toxicology by a mean of ~2 points and became worse for those with consistently positive opioid toxicology by ~4 points (Fig. 2). This reflects a ~6 point difference which is associated with a greater than 30% increased risk in 5-year mortality. Change in VACS Index 2.0 differed between those with consistently positive opioid toxicology and those with consistently negative opioid toxicology in both univariate and multivariate models (p = .004 for both; Table 3).

3.4. Change in biomarkers among PWH with suppressed HIV-1 RNA

Among PWH with suppressed HIV-1 RNA, CD4 improved among those with consistently negative opioid toxicology by a mean of ~30 cells per mm^3 and worsened for those with consistently positive opioid toxicology by a mean of ~61 cells per mm^3 (Fig. 2). Compared to those in the consistently negative trajectory group, those in the slow decrease toward negative and consistently positive groups had greater decreases in CD4, but the difference reached statistical significance only for the slow decrease toward negative group in both univariate (p = .02) and multivariate models (p = .04; Table 2). Change in log HIV-1 RNA and change in VACS Index 2.0 did not vary by opioid toxicology trajectory groups in univariate analyses or in adjusted models (overall p-values > .25).

Table 2

Association of Opioid Toxicology Trajectory Group with Patient Characteristics (n = 1815).

	Consistently Negative	Rapid Decrease toward Negative	Slow Increase toward Positive	Slow Decrease toward Negative	Consistently Positive	P-Value
N (HIV + and Uninfected)	974	276	212	181	172	
PWH Detectable HIV-1 RNA (%)	14	15	19	16	14	.6
PWH Suppressed HIV-1 RNA (%)	20	23	20	19	18	
Uninfected (%)	66	62	61	65	68	
Mean Age	53	53	53	53	53	.9
Race/Ethnicity (%)						< .001
African-American	57	73	65	77	77	
Hispanic/Other	14	13	11	8	10	
White	30	14	24	15	13	
Male (%)	99	99	99	98	100	.3
Current Smoker (%)	86	87	91	93	92	.06
Alcohol Related Diagnoses (%)	32	33	33	33	30	.9
HCV (%)	74	80	81	79	72	**.035**
Type of Treatment – Methadone (%)	61	83	75	94	94	< .001
Median Days on	582	720	243	578	472	< .001
Treatment (IQR)	(253–1276)	(319–1348)	(236–940)	(286–1072)	(226–877)	
Median # Utox	20	33	20	27	19	< .001
measures (IQR)	(11-37)	(17–49)	(12–38)	(14–43)	(10–27)	
Median Days	329	354	316	323	310	< .001
between first and last utox (IQR)	(189–353)	(269–357)	(201–350)	(237–351)	(163–347)	
Opioid Utox mean % positive (SD)	2.1 (3.5)	19.4 (9.5)	33.4 (14.6)	50.3 (14.3)	90.3 (10.1)	< .001
Marijuana Utox mean % positive (SD)	5 (18)	5 (18)	6 (17)	9 (23)	8 (21)	< .001
Cocaine Utox mean % positive (SD)	4 (15)	12 (22)	18 (29)	27 (35)	32 (40)	< .001
N for HIV + Only	326	105	82	64	55	
Baseline On ART (%)	60	58	49	66	60	.3
Start ART w/in 1 Year of Starting Treatment (%)[*]	60	52	43	55	32	.08

[*]Of those not on ART at start of treatment.

IQR = intraquartile range.

SD = standard deviation.

HCV = Hepatitis C virus.

Utox = toxicology.

ART = antiretroviral treatment.

3.5. Change in biomarkers among uninfected

Among those uninfected, mean change in VACS Index 2.0 ranged from 0.1 to 1.3 for all opioid toxicology trajectory groups and did not differ in univariate or multivariate analyses (Fig. 2, Table 3).

3.6. Sensitivity analyses

For the adjusted models above, we also ran 3 additional models to test for interactions of opioid toxicology trajectory group with year (2000–2009/2010–2015), buprenorphine treatment (yes/no), and
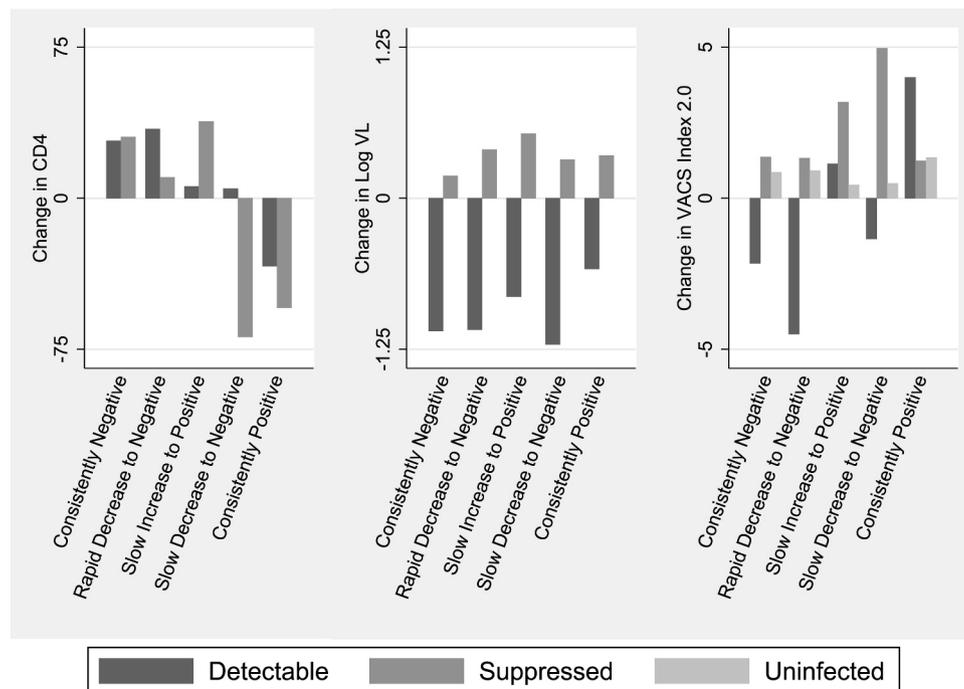

Fig. 2. Mean change in CD4, HIV-1 RNA, and VACS Index 2.0 by Opioid Toxicology Trajectory Groups and HIV and VL Status.

Table 3

Associations Between Opioid Toxicology Trajectory Groups and Change in Biomarkers Among Patients in Opioid Treatment.

Opioid Toxicology Trajectories	Coefficient[*]	95% CI
Detectable HIV-1 RNA		
CD4 change		
Consistently negative (referent group)		
Rapid decrease toward negative	5.0	− 41.8, 51.8
Slow increase toward positive	− 25.6	− 80.2, 29.0
Slow decrease toward negative	− 32.3	− 92.7, 28.1
Consistently positive	− 57.5[**]	− 113.1, 1.9
Log HIV-1 RNA change		
Consistently negative (referent group)		
Rapid decrease toward negative	0.1	− 0.4, 0.5
Slow increase toward positive	0.3	− 0.2, 0.8
Slow decrease toward negative	0.0	− 0.5, 0.6
Consistently positive	0.5[**]	0.0, 1.1
VACS Index 2.0 change		
Consistently negative (referent group)		
Rapid decrease to negative	− 1.7	− 6.2, 2.8
Slow increase to positive	3.7	− 1.7, 9.2
Slow decrease to negative	1.5	− 5.3, 8.3
Consistently positive	8.6[**]	2.8, 14.3
Suppressed HIV-1 RNA		
CD4 change		
Consistently negative (referent group)		
Rapid decrease toward negative	− 2.9	− 61.6, 55.9
Slow increase toward positive	15.2	− 48.2, 79.1
Slow decrease toward negative	− 73.7[**]	− 143.7, − 3.7
Consistently positive	− 60.0	− 130.9, 10.9
Log HIV-1 RNA change		
Consistently negative (referent group)		
Rapid decrease toward negative	0.1	− 0.2, 0.3
Slow increase toward positive	0.2	− 0.0, 0.5
Slow decrease toward negative	0.0	− 0.3, 0.3
Consistently positive	0.2	− 0.1, 0.5
VACS Index 2.0 change		
Consistently negative (referent group)		
Rapid decrease toward negative	0.8	− 2.6, 4.3
Slow increase toward positive	1.4	− 2.4, 5.2
Slow decrease toward negative	3.4	− 1.0, 7.9
Consistently positive	0.1	− 4.4, 4.5
Uninfected		
VACS Index 2.0 change		
Consistently negative (referent group)		
Rapid decrease toward negative	− 0.1	− 1.4, 1.2
Slow increase toward positive	− 0.6	− 2.0, 0.8
Slow decrease toward negative	− 0.9	− 2.6, 0.8
Consistently positive	0.3	− 1.3, 1.9

  [*] Models adjusted for age and race/ethnicity; opioid toxicology trajectory group variable included as categoral variable; coeficients represent annualized changes relative to the consistently negative group.

  [**] p < .05.

baseline value of corresponding outcome. The only statistically significant interaction was for receipt of buprenorphine and CD4 in those with detectable HIV-1 RNA; however, the number receiving buprenorphine was small (< 6) in all of the opioid toxicology trajectory groups except the consistently negative group. Models run without normalizing outcomes for time between pre and post OAT initiation

yielded similar results. We also reran the analysis restricting to those with HCV; patterns were similar. When adjusted models also included year, OAT type, and baseline value for corresponding outcome, patterns were similar although attenuated for CD4 and log HIV-1 RNA change among those with detectable HIV-1 RNA and for CD4 change among those with suppressed HIV-1 RNA. Lastly, for models using the trajectory variable that excluded the urine toxicology values that occurred after the post biomarker, results were similar but slightly attenuated for the CD4 change model for those with detectable HIV-1 RNA.

4. Discussion

Of these PWH and uninfected patients receiving OAT, over half had consistently negative opioid urine toxicology test results during treatment. Among those with suppressed HIV-1 RNA at baseline, those with consistently negative opioid toxicology had improved CD4 whereas those with consistently positive opioid toxicology had declining/worsening CD4. This finding is important as it provides a metric for the health impact of OAT that can be assessed among those with suppressed HIV-1 RNA. Among those with detectable HIV-1 RNA at baseline, consistently negative opioid toxicology was associated with improvement in CD4, HIV-1 RNA, and VACS Index 2.0 and these changes differed from those with consistently positive opioid toxicology.

We were expecting VACS Index 2.0 to correlate with opioid toxicology among PWH (suppressed and detectable HIV-1 RNA) and uninfected patients, but an association was evident only among those with detectable HIV-1 RNA. It is possible that our timeframe was not long enough to detect changes in some of the lab measurements that comprise the VACS Index 2.0. Many of those with baseline detectable HIV-1 RNA had an improvement in HIV-1 RNA and CD4 contributing to their change in VACS Index 2.0. However, for those with suppressed HIV-1 RNA at baseline, many would remain suppressed during OAT; thus HIV-1 RNA would not contribute to change in VACS Index 2.0. For those uninfected, obviously, neither a change in HIV-1 RNA or CD4 would impact VACS Index 2.0.

Our findings should be considered in light of literature assessing the impact of substance use and substance use disorder treatment on health outcomes (McLellan et al., 2014; Quinn et al., 2017). Park and colleagues reported that drug abstinence was associated with a greater decrease in adverse drug use consequences (Short Inventory of Problems, depressive symptoms, and health-related quality of life) compared to those who continued or increased drug use (Park et al., 2015). While Park and colleagues used self-reported measures for drug use and adverse drug use consequences, our study differs in that it used objective biological measures and was limited to individuals with opioid use disorder. No other studies that we are aware of have used trajectory models to identify distinct groups that estimate levels and patterns of opioid use based on opioid toxicology tests. Opioid urine toxicology tests, while objective, are limited by the fact that they reflect a relatively brief window (72 h) of detection and are not able to differentiate density of opioid use. As such, periods of "abstinence" may include episodic but undetected opioid use. Similarly, periods of positive urine toxicology may reflect intermittent low level opioid use. Biomarkers that reflect overall health may provide a more accurate assessment of OAT treatment's impact on health than episodic urine testing.

Illicit drug use has myriad direct and indirect physiologic effects, especially in PWH. Among those using opioids, liver complications can result from hepatitis [(HCV and hepatitis B (HBV)], excess acetaminophen ingestion when co-formulated with prescription opioids, and granulomatosis (talc injection) (Saitz, 2009). Kidney complications can result from glomerulonephritis (HCV), focal and segmental glomerular sclerosis (HIV), rhabdomyolysis due to intoxication or overdose, and viral hepatitis-associated nephrotic syndrome (HBV, HCV). Opioids, and in some circumstances OAT, can have direct and adverse impacts on the immune and endocrine systems as well.

In addition, drug use is associated with poor adherence to

medication, nutrition, and self-care (Lasser et al., 2011; Saitz et al., 2004, 2005). These indirect effects of drug use are evident in patients who manifest clinical findings of untreated viral hepatitis, poorly controlled medical conditions (e.g. hypertension, diabetes, asthma, heart disease), poor nutrition, and dehydration in the setting of active drug use. In addition, drug use can be associated with unstable housing situations and limited social support, manifesting in decreased access to medical care and initiation of ART (Perez-Hoyos et al., 2003; Poundstone et al., 2001). Finally, substance use is associated with receipt of lower quality HIV treatment (Ding et al., 2005), and fewer HIV quality of care indicators (Korthuis et al., 2012).

There are limitations to this research. Most patients included in our analyses were male, the majorty was HCV infected (a common co-morbidity among PWID who have opioid use disorder), and all were veterans who received medical care in the VA system. Therefore, we recommend research that attempts to replicate our findings in diverse populations including a larger proportion of women. Our measure of abstinence was opioid urine toxicology tests collected during routine clinical care so patients had differing numbers of tests and different timeframes between testing; however for the two most extreme abstinence groups (consistently negative and consistently positive), the number of tests and time between testing was similar. Patients with evident illicit drug use, including prior positive opioid tests, may have received increased surveillance resulting in more frequent opioid toxicology tests. However, this does not appear to be the case in our sample; those who were in the non-consistent groups appear to have received more frequent surveillance. Finally, components of VACS Index 2.0 were not available for all individuals who initiated OAT; this could be due to lack of engagement in care in the VA, receiving routine care outside of the VA setting, and/or because not all laboratory values were extracted from the EMR due to technical issues (McGinnis et al., 2009).

Our work has implications for future research and policy. Treatments for substance use disorders are often evaluated based on their ability to impact retention in treatment and abstinence. Less attention is paid to the impact of treatment on patient reported outcomes such as changes in patient satisfaction, functional status or on measures of health partly because there are few validated and objective measures of these outcomes. Our findings indicate that changes in CD4 among PWH with both suppressed and detectable HIV-1 RNA, and changes in viral load and VACS Index 2.0 only among PWH with detectable HIV-1 RNA may provide an objective measure of some of the health benefits of OAT; these outcomes may be useful only for specific PWH subsets as an outcome for observational and clinical trial research in the field, as well as in the Food and Drug Administration approval process for medications to treat opioid use disorder.

5. Conclusions

Trajectory models are useful for identifying distinctive longitudinal patterns of opioid urine toxicologies for those receiving OAT. These patterns are reflected by changes in CD4, HIV-1 RNA, and VACS Index 2.0 among PWH with detectable HIV-1 RNA. Among those with suppressed HIV-1 RNA, patterns were reflected only by changes in CD4. Among those uninfected, changes in opioid toxicology tests were not reflected by changes in VACS Index 2.0. Identifying biomarkers that reflect changes in opioid use is important for both future research and to clinicians. Studies are needed to extend this work and find other biomarkers, perhaps reflecting immune, neurologic, or nutritional factors, that are sensitive to changes in opioid use.

Author disclosures

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Contributors

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Conflicts of Interest

None.

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