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Hepatic safety of buprenorphine in HIV-infected and uninfected patients with opioid use disorder: The role of HCV-infection

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Abstract

Introduction—Individuals with HIV and hepatitis C (HCV) infection, alcohol use disorder, or who are prescribed potentially hepatotoxic medications may be at increased risk for buprenorphine (BUP) associated hepatotoxicity.

Materials and methods—We examined a cohort of HIV-infected and uninfected patients receiving an initial BUP prescription between 2003 and 2012. We compared changes in alanine

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and aspartate aminotransferases (ALT and AST) and total bilirubin (TB) stratified by HIV status. We identified cases of liver enzyme elevation (LEE), TB elevation (TBE), and conducted chart review to assess for cases of drug induced liver injury (DILI) and death. We examined associations between age, sex, race, HIV-infection, HCV-infection, alcohol use disorder, and prescription of other potentially heptatotoxic medications with the composite endpoint of LEE, TBE, and DILI.

Results—Of 666 patients prescribed BUP, 36% were HIV-infected, 98% were male, 60% had RNA-confirmed HCV infection, 50% had a recent diagnosis of alcohol use disorder, and 64% were prescribed other potentially hepatotoxic medications. No clinically significant changes were observed in median ALT, AST and TB and these changes did not differ between HIV-infected and uninfected patients. Compared with uninfected patients, HIV-infected (OR 7.3, 95% CI 2.1-26.1, p=0.002), HCV-infected (OR 4.9 95% CI 1.6-15.2, p=0.007) or HIV/HCV co-infected patients (OR 6.9, 95%CI 2.1-22.2, p=0.001) were more likely to have the composite endpoint of LEE, TB elevation or DILI, in analyses that excluded 60 patients with evidence of pre-existing liver injury. 31 patients had LEE, 14/187 HIV-infected and 17/340 uninfected (p = 0.25); 11 had TBE, including 9/186 HIV-infected and 2/329 uninfected (p = 0.002); 8 experienced DILI, 4/202 HIV-infected and 2/404 uninfected (p = 0.45). There were no significant associations with alcohol use disorder or prescription of other potentially hepatotoxic medications after adjustment for HIV/HCV status.

Conclusions—Liver enzymes and TB are rarely elevated in HIV-infected and uninfected patients receiving BUP. Risk of hepatotoxicity was greater in individuals infected with HIV, HCV, or HIV/HCV co-infection, who may benefit from increased monitoring.

Keywords

buprenorphine; HIV; Hepatitis C; drug induced liver injury

1. Introduction

Buprenorphine (BUP), a partial opioid agonist at the mu opioid receptor, is an effective treatment for opioid use disorder in both HIV-infected and uninfected individuals. (D. A. Fiellin et al., 2006; David A. Fiellin et al., 2011; Gowing, Ali, & White, 2009; Gowing, Farrell, Bornemann, Sullivan, & Ali, 2011; L. E. Sullivan et al., 2006; Tetrault et al., 2012; Weiss et al., 2011). BUP is a thebaine derivative and as such may be hepatotoxic, particularly in patients infected with hepatitis C virus (HCV). However, studies on BUP and hepatotoxicity have been scant, often have had small sample sizes, lacked assessment of important factors (e.g. alcohol, chronic HCV status, HIV status, prescription of other potentially hepatotoxic medications), or have been based on analyses of cases.

Early clinical studies suggested that BUP may increase liver enzymes, prompting recommendations to monitor liver enzymes in patients receiving BUP. (Lange, Fudala, Dax, & Johnson, 1990) Some clinicians are concerned about the safety of BUP in their HIV-infected patients, who often have chronic HCV co-infection, may have alcohol use, and are often prescribed other medications (e.g., statins) that may also increase the risk of acute live injury with BUP use. (Edelman et al., 2013; Sullivan, Tetrault, Bangalore, & Fiellin, 2006) A recent prospective cohort study demonstrated that clinically significant hepatotoxicity

rarely occurs in HIV-infected individuals receiving BUP. (Vergara-Rodriguez et al., 2011) This study, however, did not include an HIV-uninfected comparator group and had limited information on concomitant liver disease, alcohol use, or exposure to other potentially hepatotoxic medications. A recent randomized controlled trial investigated changes in markers of liver health in patients receiving BUP or methadone and observed no significant difference between the two groups in likelihood of transaminase elevation. (Saxon et al., 2013) In this study it was noted that "extreme" liver enzyme elevation [defined in this study as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of greater than 10 times upper limit of normal, total or direct bilirubin greater than 2 mg/dL, or maximum international normalized ratio (INR) of greater than 1.5] was more likely to occur in patients who sero-converted to hepatitis B or C virus infection during the study or who continued to use illicit drugs. Notably, fewer than two percent of participants in this study had HIV infection. (Saxon et al., 2013) Similarly, data from a 12-month observational cohort study of patients receiving BUP confirmed that BUP is relatively safe with regard to potential liver injury. (Soyka, Backmund, Schmidt, & Apelt, 2014)

In vitro studies suggested that BUP is a proton donor which at high concentrations may interfere with mitochondrial respiration resulting in necrosis of hepatocytes. (Berson, Fau, et al., 2001) One early, relatively small study of patients receiving BUP obtained transaminase levels on patients prior to medication initiation and again after a minimum of 40 days. (Petry, Bickel, Piasecki, Marsch, & Badger, 2000) Patients with viral hepatitis (not otherwise specified), compared to those without, exhibited statistically significant, but not necessarily clinically meaningful, increases in ALT (median increase=8.5 IU) and AST (median increase=9.5 IU). In this study, higher BUP doses were associated with greater odds of an increase in AST, suggesting a dose response relationship. In addition, acute liver transaminase elevation has been seen in HCV-infected individuals who inject BUP intravenously. (Berson, Gervais, et al., 2001) One case series reported on 7 patients with HCV infection who developed acute liver transaminase elevation while receiving BUP. (Herve et al., 2004) A more recent case series, however, of 4 patients with acute HCV infection and elevated liver enzymes, found no change in liver enzyme values during BUP treatment. In fact, liver enzymes improved.(Bruce & Altice, 2007) These studies suggest that although liver enzyme changes may occur among patients with HCV infection, especially those misusing BUP, the clinical significance of these changes is unclear.

It is widely recognized that liver enzyme changes can also occur in patients with alcohol use. Therefore it is important to assess the impact of BUP on liver enzymes in patients with co-occurring alcohol use disorder. Additionally, HIV-infected patients are often prescribed medications that may lead to liver enzyme elevation and/or elevated total bilirubin. This includes antiretroviral medications or medications prescribed to address the adverse effects of antiretrovirals or concurrent comorbidities (i.e., statins for hyperlipidemia).

Further information is necessary to fully understand the clinical significance of changes in measures of liver health in HIV-infected and uninfected patients prescribed BUP for opioid use disorder. Therefore, the purpose of this paper is to investigate the impact of BUP on liver enzymes, total bilirubin (TB), and drug induced liver injury (DILI) among individuals with

HIV, HCV, and alcohol use disorder, who may be receiving other potentially hepatotoxic medications using data from the Veterans Aging Cohort Study.

2. Materials and methods

2.1 Source population and study design

The data source for this cohort of patients prescribed BUP was the Veterans Aging Cohort Study- (VACS). The VACS is a database of longitudinal electronic health record, pharmacy, and laboratory data of HIV-infected and matched uninfected comparators. Full details of VACS have been described elsewhere.(Fultz et al., 2006)

2.2 Study sample

Potential patients for this analysis were identified from 125 VA sites nationwide, entered VACS by 2012, and were alive in 2003 (30,167 HIV-infected, 80,862 uninfected). We included patients who received a prescription of sublingual BUP (buprenorphine or buprenorphine/naloxone) of at least 7 days duration between 2003-2012. We restricted our analysis to include only the first cycle of BUP to avoid enriching our sample with patients who had prior BUP exposure. We excluded patients in whom we did not have ALT, AST, or TB information before or after BUP initiation.

2.3 Variables

Variables included in our analysis were gender, age, and race/ethnicity; HIV status; evidence of HCV infection (classified as RNA confirmed, antibody positive only, or no evidence of HCV); alcohol use disorder diagnosis (consistent with alcohol abuse or dependence based on ICD-9 codes) classified by time frame since diagnosis (within prior year, prior 2-5 years, more than 5 years, or no diagnosis); prescription of other potentially hepatotoxic medications (nevirapine, tipranavir, delavirdine, efavirenz, ritonavir, azithromycin, clarithromycin, fluconazole, isoniazid, itraconazole, ketoconazole, rifabutin, rifampin, voriconazole, statins, and acetaminophen); measures of liver health: ALT, AST, and TB; and BUP dose and duration.

2.3.1 Definitions for liver enzyme elevation, TB elevation and drug induced liver injury—We examined liver enzyme elevation (LEE) events, which we defined as any ALT or AST, measured during the 365 days following BUP initiation, that was >5 times baseline (baseline for each patient was defined as the average of all available lab data in the year prior to BUP prescription) or >3.5 times baseline if baseline was >40 U/L (normal range for ALT = 9 to 60 U/L, normal range for AST = 10 to 40U/L). If baseline ALT or AST was missing we used a cutoff of 200 to define LEE. We also looked for TB elevation (TBE) which we defined as 2 times the upper limit of normal (0.2-1.2 mg/dL). (Cicconi et al., 2007) Finally, we also evaluated cases of drug-induced liver injury (DILI) based on ICD-9 coding, DILI requiring hospitalization, or DILI apparently resulting in death. Cases of DILI resulting in hospitalization or death were identified by the following ICD-9 codes: 573.3, 573.8, 570, 572.2, 572.4, 572.8, V42.7. (Lo Re et al., 2013) Cases of DILI and death were further evaluated by a clinician's chart review, which included review of other potentially hepatotoxic medications and other potential causes of hepatic injury and death.

2.4 Data Analysis

Summary statistics were used to describe sample characteristics. Because we were most interested in identifying LEE, TBE, and DILI that might be attributable to BUP, we excluded from primary analysis patients who had evidence of pre-existing events, as is standard pharmacoepidemiological practice. However, because patients with pre-existing liver injury might be particularly vulnerable to clinically relevant liver problems and may still be prescribed BUP, we conducted a parallel, alternate analysis without this exclusion to examine differences. We determined each patient's average level of ALT, AST and TB in the 365 days preceding initiation of BUP, and again in the 365 days following BUP initiation. The difference between these individual pre- and post-averages was used to assess median change in liver enzymes and TB, stratified by HIV status. We also examined differences in outcomes of LEE, TBE, DILI and the composite endpoint of LEE, TBE, and DILI by HIV status. Differences were considered statistically significant if *p*-value for comparison by HIV status was <0.05, using the Wilcoxon test. We examined bivariate associations between variables listed above and the composite endpoint of LEE, TB, or DILI. We then used multivariable logistic regression to model these associations adjusting for age, and other variables that remained significant or confounded associations with HIV and HCV status. All analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1 Characteristics of the study sample

Of 666 patients enrolled in VACS who were initially prescribed BUP during the predefined study time frame, 36% were HIV-infected (Table 1). Ninety-eight percent were male, the median age was 53 years (IQR 48-56), and 35% were white. Seventy-one percent had evidence of HCV infection (60% HCV RNA-confirmed, 11% antibody positive or HCV RNA negative or status unknown), 50% had a recent alcohol use disorder diagnosis and 64% were prescribed other potentially hepatotoxic medications. The median dose of BUP was 10 mg (IQR 8-16), and the median duration of exposure was 141 days (IQR 40-356), corresponding to 336 person-years of BUP exposure. Concomitant HCV infection and prescription of other potentially hepatotoxic medications were more common in HIV-infected patients. Pre-existing liver injury was evident in 40 (16.5%) of HIV-infected and 20 (4.7%) of uninfected patients (p<.001). LEE, TBE and DILI were more common in HIV-infected than uninfected patients (p <0.05 for all).

3.2 Median change in transaminases and total bilirubin

There were 539 patients (482 after excluding those with pre-existing liver injury) with ALT and AST measurements before and after initiation of BUP (pre- and post-BUP); and 541 (485 after excluding those with pre-existing liver injury) with TB measurements pre- and post-BUP. Patterns of pre- and post-BUP lab availability were similar for liver enzymes and TB, and for patients with or without pre-existing liver injury. Patients with HIV infection (87% vs 76%), HCV infection (84% vs 76%), recent diagnosis of alcohol use disorder (83% vs 72%) and other potentially hepatotoxic medication (87% vs 67%) were more likely to have complete labs than those without. Among those without evidence of pre-existing liver injury, there were no clinically meaningful changes in ALT, AST or TB (Table 2), despite a

statistically significant difference in the distribution of TB change by HIV status. Nor were there clinically meaningful changes when we did not exclude pre-existing liver injury.

3.3 Liver enzyme elevation and total bilirubin elevation

Among 606 patients without pre-existing liver injury, 527 had lab values for LEE and 515 for TBE. Patients with HIV infection (93% vs 84%), HCV infection (90% vs 84%), recent diagnosis of alcohol use disorder (87% vs 81%) and other potentially hepatotoxic medication (93% vs 77%) were more likely to have complete labs than those without. Seventeen cases of ALT elevation occurred, 6 among HIV-infected and 11 among uninfected patients (p=0.99); 21 cases of AST elevation occurred, 11 among HIV-infected and 10 among uninfected patients (p=0.10); 31 cases of either ALT or AST elevation occurred, 14 among HIV-infected and 17 among uninfected patients (p=025) (Table 3). An additional 7 LEE cases were identified in those with pre-existing liver injury. Of the 38 total cases, 45% were HIV-infected, 87% HCV-infected, 58% had diagnosed alcohol use disorder in the prior year and 71% received a potentially hepatotoxic medication. Eleven cases of TB elevation occurred, 9 among HIV-infected and 2 among uninfected patients, (p=0.002). Without exclusion of pre-existing liver injury, 15 more cases of TBE occurred, 13 in HIV-infected and 2 in uninfected patients. Of the 26 total cases of TBE all had either HIV or HCV infection, 85% were HIV-infected, 73% were HCV-infected, 58% had diagnosed alcohol use disorder in the prior year and 81% received a potentially hepatotoxic medication.

3.4 Drug induced liver injury and death

Based on ICD-9 coding and clinician chart review, 8 cases of DILI occurred (4 in HIV-infected and 4 in uninfected patients, p=0.45) among 606 patients without pre-existing liver injury. An additional 6 cases of DILI were identified among 60 patients with pre-existing liver injury (5 in HIV-infected and 1 in uninfected patients. Among 14 total cases of DILI, 64% were HIV-infected, 86% HCV-infected, 57% had diagnosed alcohol use disorder in the prior year and 93% received a potentially hepatotoxic medication. Therefore, 2% of all patients prescribed BUP experienced DILI. Two cases were hospitalized, both among patients with HIV/HCV co-infection.

A total of 11 deaths (2%) occurred in patients without pre-existing liver injury during the period of observation (3 in HIV-infected, and 8 in uninfected patients). An additional 3 deaths occurred in those with pre-existing liver injury, 1 in HIV-infected and 2 in uninfected patients. Among the 14 deaths, 29% were HIV-infected, 86% HCV-infected, 64% had diagnosed alcohol use disorder in the prior year and 50% received a potentially hepatotoxic medication. Therefore, 2% of all patients died in the 365 days after starting BUP. Cause of death for 8 patients could be evaluated by clinician chart review, none were related to BUP or DILI.

3.5 Associations with composite endpoint of LEE, TB elevation, or DILI

Because there was considerable overlap in LEE, TBE and DILI we created a composite endpoint. We observed 44 events in those without pre-existing liver injury and another 26 in those with pre-existing liver injury. In bivariate analysis, HIV infection, HCV infection and prescription of other hepatotoxic medications were associated with the composite endpoint

(Table 4). Therefore, these variables and age were included in logistic regression analysis (Table 5). Our final model revealed that HIV infection (OR 7.3, 95% CI 2.1-26.1), HCV infection (OR 4.9, 95% CI 1.6-15.2), and HIV/HCV co-infection (OR 6.9, 95% CI 2.1-22.2) were associated with the composite endpoint of LEE, TB elevation, or DILI among patients prescribed BUP. Results were similar when we included those with pre-existing liver injury.

4. Discussion

In our clinical sample of HIV-infected and uninfected individuals receiving BUP, there was no substantive change in AST, ALT or TB in either HIV-infected or uninfected patients. When LEE did occur, it was equally likely in HIV-infected and uninfected patients. TB elevation was more likely to occur in HIV-infected patients. Additionally, both alcohol use disorder and prescription of other potentially hepatotoxic medications had less of an impact on measures of liver health than did HIV infection, HCV infection, or HIV/HCV co-infection in this cohort.

Our findings confirm those of a recent prospective cohort study that followed over 300 HIV-infected patients prescribed BUP. That study observed no clinically significant increases in AST or ALT, even when the analysis was restricted to patients with HIV and HCV co-infection.(Vergara-Rodriguez et al., 2011) However, our study includes an HIV-uninfected comparator group, which allowed us to detect subtle differences in AST, ALT and TB due to HIV disease; included information on alcohol use disorder and prescription of other potentially hepatotoxic medications; and also evaluated the development of marked LEE and TB elevation, DILI and death.

A recent trial randomized 1269 participants to receive either BUP or methadone for 24 weeks and monitored laboratory indices of liver health. (Saxon et al., 2013) In this study, changes in transaminase levels were no different between patients receiving BUP or methadone. Hepatitis B and HCV infection were each associated with such increases. “Extreme” liver elevations (defined as ALT or AST elevation> 10 times the upper limit of normal, total bilirubin > 2 mg/dL, direct bilirubin > 2 mg/dL, or maximum international normalize ratio > 1.5) were noted in both groups (2.1% in the BUP group and 3.6% in the methadone group) and were more likely to occur in patients who sero-converted to hepatitis B or C or who had ongoing illicit drug use during the first 8 weeks of the study. The authors of this study concluded that although liver injury occurs rarely in association with BUP, given the high prevalence of liver disease in this population, periodic measurements of liver enzymes and TB are reasonable. (Saxon et al., 2013) Similar results were noted among pregnant women with opioid use disorder followed in the MOTHER study comparing BUP and methadone; liver enzymes remained stable in both the treatment groups, with increases noted only in participants with HCV infection. (McNicholas et al., 2012) Other studies have also suggested periodic liver enzyme monitoring in patients treated with BUP, especially if they have underlying HCV. (Petry et al., 2000) Recent pharmacokinetic data suggest that HCV-seropositivity is associated with higher plasma concentrations of buprenorphine and its metabolites, suggesting an increased bioavailability of BUP or diminished clearance of BUP and its metabolites in the presence of HCV infection, even in the absence of active liver disease. (Masson, Rainey, Moody, & McCance-Katz, 2014) Although liver enzymes were

elevated among those with HCV infection compared with those without HCV infection in this study, these elevations were not clinically significant. (Masson et al., 2014)

Our study results are in contrast to prior case reports suggesting acute liver enzyme elevation in patients with HCV treated with or misusing BUP. (Berson, Gervais, et al., 2001; Herve et al., 2004) In addition to patients with active HCV infection, a case report described acute symptomatic liver and kidney failure in a patient with positive HCV antibody but non-detectable HCV viral load treated with standard doses of BUP. Discontinuation of BUP led to resolution of both kidney and liver dysfunction in this patient. (Zuin et al., 2009) Additionally, a case report of acute, clinically significant liver enzyme elevation has been reported in an adolescent receiving high dose BUP without any evidence of underlying liver disease, including viral hepatitis. (Upadhyay & Xueming, 2010)

Our study has several limitations. First, because the data are observational and routine serial blood work was not performed in all patients, we were only able to detect cases of LEE, TB elevation and DILI measured in the course of clinical care. It is possible that some elevations went undetected, however it is unlikely that elevations that would have reached our threshold (up to 5 times normal) would be missed on routine lab draws. Transient elevations may have occurred between lab draws but would be unlikely to be clinically significant. Also, because this cohort is based on individuals who were receiving care in the Veterans Health Administration, few women are included. We were not able to assess adherence to the BUP that was not dispensed through a VA pharmacy. Lastly, we relied on ICD-9 coding and as such, our study may underestimate risk of DILI due to reliance on coding.

5. Conclusions

Our study among a group of HIV-infected and uninfected patients prescribed BUP and with a high prevalence of HCV infection, diagnosis of alcohol use disorder and prescription of other potentially hepatotoxic medications adds to the growing literature of BUP's hepatic safety profile in patients with and without HIV infection. Although LEE, TB elevation and DILI did occur, these cases were relatively uncommon and, not surprisingly, were more likely to occur in patients with evidence of HIV infection, HCV infection, or HIV/HCV co-infection. Therefore, periodic and/or symptom triggered monitoring of liver enzymes and TB is prudent in patients prescribed BUP. Based on these data, however, recommendations for frequency of testing cannot be determined. Most importantly, underlying liver disease should not preclude patients from receiving this medication; rather, these patients may need more frequent monitoring.

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Highlights

- We compare changes in alanine and aspartate aminotransferases (ALT and AST) and total bilirubin (TB) before and 365 days after buprenorphine prescription among a clinical cohort of patients with and without HIV infection.
- No clinically significant changes were observed in median ALT, AST and TB among HIV-infected and uninfected patients in the Veteran's Aging Cohort Study who were prescribed buprenorphine and these changes did not differ between the two groups.
- Compared with uninfected patients, HIV-infected (OR 7.3, 95% CI 2.1-26.1, p=0.002), HCV-infected (OR 4.9 95% CI 1.6-15.2, p=0.007) or HIV/HCV co-infected patients (OR 6.9, 95%CI 2.1-22.2, p=0.001) prescribed buprenorphine were more likely to have the composite endpoint of liver enzyme elevation, total bilirubin elevation, or drug induced liver injury. There were no significant associations with alcohol use disorder or prescription of other potentially hepatotoxic medications after adjustment for HIV/HCV status.
- Liver enzymes and TB are rarely elevated in HIV-infected and uninfected patients receiving BUP. Risk of hepatotoxicity was greater in individuals infected with HIV, HCV, or HIV/HCV co-infection, who may benefit from increased monitoring.

Table 1

Characteristics of study sample, N=666

Characteristic	HIV-infected (N=242)	Uninfected (N=424)	Total (N=666)	p*
Gender, male n, (%)	236 (97.5)	415 (97.9)	651 (97.7)	0.77
Age, median (IQR)	54 (50-57)	52 (47-56)	53 (48-56)	0.002
Race				
-White, non-Hispanic n (%)	70 (28.9)	160 (37.7)	230(34.5)	0.05
-Black, non-Hispanic n (%)	134 (55.4)	215 (50.7)	349 (52.4)	
-Other n (%)	38 (15.7)	49 (11.6)	87 (13.1)	
HCV infection, n (%)				
-RNA confirmed	177 (73.1)	225 (53.1)	402 (60.4)	<0.0001
-Antibody positive	25 (10.3)	47 (11.1)	72 (10.8)	
-No evidence	40 (16.5)	152 (35.8)	192 (28.8)	
Alcohol use disorder, n (%)				
-Prior year	118 (48.8)	212 (50.0)	330 (49.5)	0.16
-Prior 2-5 years	52 (21.5)	84 (19.8)	136 (20.4)	
-More than 5 years ago	34 (14.0)	48 (11.3)	82 (12.3)	
-No evidence	38 (15.7)	80 (18.9)	118 (17.7)	
Prescribed other potentially hepatotoxic medications, n (%)	198 (81.8)	228 (53.8)	426 (64.0)	<0.001
Pre-existing liver injury				
-Liver enzyme elevation	14 (5.8)	11 (2.6)	25 (3.8)	0.04
-Total bilirubin elevation	25 (10.3)	6 (1.4)	31 (4.7)	<0.001
-Drug induced liver injury	8 (3.3)	4 (0.9)	12 (1.8)	0.04
-Any injury	40 (16.5)	20 (4.7)	60 (9.0)	<0.001
BUP dose, mg/day, median (IQR)	11 (8-16)	10 (8-16)	10 (8-16)	0.50
BUP duration, days, median (IQR)	131 (42-358)	147 (39-354)	141 (40-356)	0.88
Person-years of BUP prescription	124	212	336	

*Wilcoxon or Chi-square test, comparing HIV-infected to uninfected

Table 2

Median (IQR) change in liver enzymes and total bilirubin, as difference between each individual's average value for 365 days before buprenorphine initiation and average value for 365 days after buprenorphine initiation

	Primary Analysis, N=606 Excluding pre-existing liver injury			Alternate Analysis, N=666 Not excluding pre-existing liver injury		
Liver enzymes	**HIV-infected (N=175)**	**Uninfected (N=307)**	**p***	**HIV-infected (N=214)**	**Uninfected (N=325)**	**P***
ALT	0.7 (-7.6, 12.5)	1 (-6, 8.5)	0.75	-0.8 (-9.9, 10.7)	0.5 (-6.8, 8.5)	0.51
AST	1 (-7.1, 11.2)	0.5 (-5, 8.1)	0.52	0.2 (-10.2, 8.8)	0.2 (-5.5, 8)	0.70
Total Bilirubin	(N=202)	(N=310)		(N=214)	(N=327)	
TB	0 (-0.1, 0.2)	0 (-0.2, 0.1)	0.03	0 (-0.2, 0.2)	0 (-0.2, 0.1)	0.54

*Wilcoxon test, comparing HIV-infected to uninfected

Table 3

a. Outcomes by HIV status of 606 patients, *excluding* pre-existing liver injury, during the first 365 days of buprenorphine prescription (patients may have more than one outcome). N (%)

	HIV-infected (N = 202)		Uninfected (N = 404)		Total Sample (N = 606)		p*
Liver enzymes available after BUP initiation	187	(92.6)	340	(84.2)	527	(87.0)	0.004
ALT elevation	6	(3.2)	11	(3.2)	17	(3.2)	0.99
AST elevation	11	(5.9)	10	(2.9)	21	(4.0)	0.10
Either ALT or AST elevation	14	(7.5)	17	(5.0)	31	(5.9)	0.25
TB available after BUP initiation	186	(92.1)	329	(81.4)	515	(85.0)	0.001
TB elevation	9	(4.8)	2	(0.6)	11	(2.1)	0.002
Drug Induced liver injury (DILI)	4	(2.0)	4	(1.0)	8	(1.3)	0.45
Compostie endpoint (Elevation of ALT, AST, TB; or DILI)	24	(11.9)	20	(5.0)	44	(7.3)	0.002

b. Alternate analysis, outcomes by HIV status of 666 patients, not excluding pre-existing liver injury, during the first 365 days of buprenorphine prescription (patients may have more than one outcomes). N (%)

	HIV-infected (N = 242)		Uninfected (N = 424)		Total sample (N = 666)		P
Liver enzymes available after BUP initiation	226	(93.4)	358	(84.4)	584	(87.7)	0.001
ALT elevation	7	(5.8)	14	(3.4)	21	(4.3)	0.61
AST elevation	13	(4.9)	12	(2.8)	25	(3.6)	0.16
Either ALT or AST elevation	17	(7.5)	21	(5.9)	38	(6.5)	0.43
TB available after BUP initiation	225	(93.0)	346	(81.6)	571	(85.7)	<0.001
TB elevation	22	(9.8)	4	(1.2)	26	(4.6)	<0.001
Drug Induced liver injury (DILI)	9	(3.7)	5	(1.2)	14	(2.1)	0.03
Composite endpoint (Elevation of ALT, AST, TB; or DILI)	44	(18.2)	26	(6.1)	70	(10.5)	<0.001

*Chi-square of Fisher exact test, comparing HIV-infected to uninfected.

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Table 4

Bivariate associations with composite endpoint of liver enzyme elevation, total bilirubin elevation or drug induced liver injury.

		Primary analysis			**Alternate analysis**		
		Excluding pre-existing liver injury			**Not excluding pre-existing liver injury**		
		At-risk N=606	**Event N=44**	**p**	**At-risk N=666**	**Event N=70**	**P**
Age	<45	343	24 (7.3)	0.54	375	41 (10.9)	0.89
	45-55	185	12 (6.5)		207	20 (9.7)	
	>55	78	8 (10.3)		84	9 (10.7)	
Sex	M	591	44 (7.4)	0.27	651	70 (10.8)	0.18
	F	15	0 (0)		15	0 (0.0)	
Race	White, non-hispanic	203	17 (8.4)	0.41	230	26 (11.3)	0.70
	Black, non- hispanic	324	24 (7.4)		349	37 (10.6)	
	Other	79	3 (3.8)		87	7 (8.0)	
History of Hepatitis C infection	RNA confirmed	353	32 (9.1)	0.13	402	56 (13.9)	0.002
	Antibody positive	69	3 (4.3)		72	3 (4.2)	
	No evidence	184	9 (4.9)		192	11 (5.7)	
HIV/HCV (RNA confirmed HCV)	HIV and HCV	143	16 (11.2)	0.002	177	34 (19.2)	<0.001
	HIV only	59	8 (13.6)		65	10 (15.4)	
	HCV only	210	16 (7.6)		225	22 (9.8)	
	Uninfected	194	4 (2.1)		199	4 (2.0)	
History of alcohol use disorder	Prior year	293	26 (8.9)	0.46	330	40 (12.1)	
	Prior 2-5 years	125	8 (6.4)		136	14 (10.3)	
	More than 5 years ago	73	3 (4.1)		82	6 (7.3)	
	No evidence	115	7 (6.1)		118	10 (8.5)	
Other hepatotoxic medications	No	226	10 (4.4)	0.04	240	14 (5.8)	0.003
	Yes	380	34 (8.9)		426	56 (13.1)	

Table 5

Final regression model of associations with composite endpoint of LEE, TB elevation, or DILI

		Primary Analysis Existing pre-existing liver injury, N=44			Alternate Analysis Not excluding pre-existing liver injury, N=70		
		OR	**95% CI**	**p**	**OR**	**95% CI**	**P**
HIVand/or HCV infection	HIV/HCV	6.9	2.1-22.2	0.001	12.7	4.2-38.2	<0.001
	HIV only	7.3	2.1-26.1	0.002	8.5	2.5-28.8	0.001
	HCV only	4.9	1.6-15.2	0.007	6.4	2.1-19.3	0.001
	Uninfected	Ref			Ref		
Age		1.0	0.9-1.0	0.047	1.0	0.9-2.0	0.040
Other hepatotoxic medications		1.7	0.8-3.7	0.170	1.9	1.0-3.6	0.060