Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2013 December ; 22(12): 1352–1356. doi:10.1002/pds.3517.

Acetaminophen Receipt Among HIV-Infected Patients with Advanced Hepatic Fibrosis

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Abstract

Purpose—HIV-infected patients may be at particular risk for acetaminophen-induced hepatotoxicity, but acetaminophen use in the context of liver injury has been incompletely examined among HIV-infected patients. Among a sample of HIV-infected patients, we aimed to determine acetaminophen exposure; assess the cross-sectional association between acetaminophen exposure and advanced hepatic fibrosis; and determine whether factors associated with acetaminophen exposure varied by HCV status.

Methods—We conducted a cross-sectional analysis of the Veterans Aging Cohort Study. Advanced hepatic fibrosis was defined as a FIB-4 > 3.25, a composite score calculated based on age, alanine aminotransferase, aspartate aminotransferase and platelet count. Multivariable ordered polytomous logistic regression was used to determine the association between FIB-4 status and acetaminophen exposure stratified by HCV status.

Results—Among HIV-infected patients (n=14,885), 31% received at least one acetaminophen prescription. Among those receiving acetaminophen, acetaminophen overuse was common among both HIV-monoinfected and HIV/HCV-coinfected patients (846 [31%] vs. 596[32%], p=0.79).

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Disclosures: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Conflicts of Interest: Dr. Fiellin has received honoraria from Pinney Associates and ParagonRx for serving on External Advisory Boards to review the diversion and abuse of buprenorphine. The authors have no additional conflicts of interest.

After stratifying by HCV status, those with evidence of advanced liver fibrosis were equally likely to be exposed to acetaminophen. Further, HIV-monoinfected patients with an alcohol use disorder were more likely to have acetaminophen overuse (OR [95% CI]=1.56 [1.21, 2.02]).

Conclusions—Strategies to minimize acetaminophen exposure, especially for HIV-monoinfected patients, are warranted.

Keywords

acetaminophen; HIV; Hepatitis C; Veterans; medication

Introduction

Acetaminophen, commonly causes liver injury,¹ especially when co-formulated with opioids.² HIV-infected patients may be particularly vulnerable to acetaminophen-induced hepatotoxicity³ given their risk of liver disease,^{2,4} high hepatitis C virus (HCV)-coinfection prevalence, possible differences in acetaminophen metabolism,^{3,5} and exposure to antiretroviral and other potentially hepatotoxic medications.⁶ While recent studies have examined acetaminophen use,⁷⁻¹¹ data focusing on HIV-infected patients are lacking.

Among a sample of HIV-infected patients, we sought to: 1) determine acetaminophen exposure; 2) assess the cross-sectional association between acetaminophen receipt and advanced hepatic fibrosis; and 3) determine whether factors associated with acetaminophen use varied by HCV status. We hypothesized that HIV-infected patients would commonly receive 2gm/day of acetaminophen despite evidence of advanced hepatic fibrosis.

Methods

We conducted a cross-sectional study of the Veterans Aging Cohort Study Virtual Cohort (VACS-VC).¹² VACS-VC includes 40,594 HIV-infected and 81,188 age/sex/race/ethnicity/site-matched uninfected patients followed in the Veterans Affairs (VA) Healthcare System. Demographic data, medical diagnoses (recorded using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes), laboratory results, and pharmacy fills are collected from electronic medical records. The Human Investigations Committees at Yale University and the VA Connecticut Healthcare System approved the study and granted a waiver of informed consent.

Our analytic sample included HIV-infected patients with laboratory and pharmacy data in fiscal year (FY) 2006. Excluded patients had: 1) a cancer diagnosis (except non-epithelial skin cancer) (n=4,017); 2) no HIV diagnosis or antiretroviral prescriptions (n=78,591); 3) no inpatient or outpatient visit in FY2006 (n=15,521); or 4) missing laboratory or pharmacy data (n=8,768).

As the majority of U.S. Veterans receive their medications from VA pharmacies,¹³ we determined receipt of all acetaminophen products from outpatient pharmacy data, including the proportion co-formulated with an opioid.¹⁴ Days of acetaminophen receipt were determined based on prescription information. Average daily acetaminophen dose was calculated by dividing the total milligrams of acetaminophen received in FY2006 by the

number of days supplied. Acetaminophen receipt was categorized as: no acetaminophen use, low dose (i.e. 0-2gm/day), and overuse (i.e. 2gm/day), consistent with recommendations that patients with existing liver disease ingest fewer than 2gm of acetaminophen daily.¹⁵ We assessed whether patients had received more than one prescription for other potentially hepatotoxic medications: 1) Non-Acetaminophen Analgesics: non-steroidal anti-inflammatory drugs; 2) Antiretroviral Agents: nevirapine, tipranavir, delavirdine; and 3) Other Potentially Hepatotoxic Medications: azithromycin, clarithromycin, fluconazole, isoniazid, itraconazole, ketoconazole, rifabutin, rifampin, voriconazole, and statins.

Socio-demographic variables included gender, age, and race/ethnicity. Clinical variables, including HCV status (using ICD-9 diagnoses and/or a positive HCV antibody or RNA result) and the presence of an alcohol use disorder (using ICD-9 codes) were assessed.

The presence of advanced hepatic fibrosis was determined based on the calculated FIB-4 score (using labs closest to the midpoint of FY2006).¹⁶ FIB-4 is calculated based on age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count.¹⁶ A FIB-4 >3.25 identifies advanced hepatic fibrosis (METAVIR stages F3-F4) with a high degree of accuracy and a specificity of 97%.¹⁶

We performed descriptive statistics. We evaluated acetaminophen daily dosage overall and stratified by FIB-4 (FIB-4 > 3.25 vs. FIB-4 ≤ 3.25), and by acetaminophen use categories. We performed multivariable ordered polytomous logistic regression to determine adjusted odds ratios (ORs) for acetaminophen receipt and FIB-4 >3.25 versus ≤ 3.25. We examined patient factors associated with acetaminophen overuse. We conducted a sensitivity analysis to determine whether findings changed with the inclusion of other potentially hepatotoxic medications. The final model included patient characteristics that were significant at p<0.05 level or clinically relevant. Results were stratified by HCV status. Analyses were performed using SAS v9.1.3 (SAS Institute Inc., North Carolina).

Results

Our analytic sample included 14,885 HIV-infected patients, 5,449 (37%) of whom were HIV/HCV-coinfected, and 1,287 (9%) of whom had a FIB-4 > 3.25. Patients were a racially/ethnically (39% white, 49% black, 8% Hispanic, 5% other) diverse sample of men (98%) with a mean age of 45 years. At least one acetaminophen prescription was received by 4,592 (31%) of patients. HIV-monoinfected patients less commonly received non-acetaminophen analgesics than HIV/HCV-coinfected patients (2,297 [24%] vs. 1,708 [31%], p<0.001). Potentially hepatotoxic antiretroviral agents were infrequently prescribed to either HIV-monoinfected patients or HIV/HCV-coinfected patients (11 [0.1%] vs. 9 [0.2%], p=0.44). Other potentially hepatotoxic medications were more commonly prescribed to HIV-monoinfected than HIV/HCV-coinfected patients (4,359 [46%] vs. 2,086 [38%], p<0.001). Among the overall sample, the most commonly received other potentially hepatotoxic medications included statins (22%), azithromycin (15%) and fluconazole (9%).

HIV-monoinfected patients less commonly received acetaminophen than HIV/HCV-coinfected patients (2,707 [29%] vs. 1,885 [34%], p<0.001). Average daily acetaminophen

dose was similar between HIV-monoinfected and HIV/HCV-coinfected patients (1.48 vs. 1.43 gm/day, $p=0.79$). Among HIV-monoinfected patients, the average daily acetaminophen dose did not differ between those with a FIB-4 ≤ 3.25 and those with a FIB-4 > 3.25 (1.50 versus 1.20 gm/day, $p=0.08$) (Figure 1a); results were similar for HIV/HCV-coinfected patients ($p=0.14$) (Figure 1b). Among those who received at least one acetaminophen prescription, 1,442 (31%) patients were dispensed ≥ 2 gm/day of acetaminophen (846[31%] HIV-monoinfected versus 596[32%] HIV/HCV-coinfected, $p=0.79$).

HIV-monoinfected patients were dispensed fewer days' supply of acetaminophen than HIV/HCV-coinfected patients (34 [IQR, 14, 132] vs. 42 [IQR, 15, 155] days; $p=0.01$). Twenty five percent of acetaminophen prescriptions were co-formulated with an opioid (2,258 [24%] HIV-monoinfected vs. 1,504 [28%] HIV/HCV-coinfected, $p<0.001$).

In the full adjusted model (Table 1), compared to patients with a FIB-4 ≤ 3.25 , those with a FIB-4 > 3.25 were less likely to have acetaminophen overuse. Factors associated with acetaminophen overuse were HIV/HCV-coinfection, alcohol use disorders, and both acute, and chronic-pain related diagnoses. Patients with Hispanic ethnicity were less likely to have acetaminophen overuse. When non-acetaminophen analgesics, potentially hepatotoxic antiretroviral agents and other potentially hepatotoxic medications were included in the model, the results were not substantially different.

When stratified by HCV status, compared to patients with a FIB-4 ≤ 3.25 , both HIV-monoinfected and HIV/HCV-coinfected patients with a FIB-4 > 3.25 were as likely to have acetaminophen overuse. Findings from the full model persisted among the subgroup of patients with HIV-monoinfection. Among patients with HIV/HCV-coinfection, however, the presence of an alcohol use disorder was no longer associated with acetaminophen overuse, while older patients and males were less likely to have acetaminophen overuse.

Discussion

We found that approximately one third of HIV-monoinfected and HIV/HCV-coinfected patients received acetaminophen, commonly co-formulated with an opioid. Patients with evidence of advanced liver fibrosis were less likely to receive ≥ 2 gm/day of acetaminophen compared to those without; a finding which did not persist in the stratified models. Moreover, patients with HCV-coinfection and alcohol use disorders were 25% and 28%, respectively, more likely to receive ≥ 2 gm/day. Notably, we found that HIV-monoinfected patients with an alcohol use disorder were 56% more likely to receive ≥ 2 gm/day. These data suggest that HIV-infected patients are commonly exposed to high doses of acetaminophen despite risk factors for acetaminophen-induced hepatotoxicity. This may be explained by their relatively high prevalence of painful conditions,^{17,18} which may be exacerbated by chronic HCV and alcohol use disorders, limited treatment options, and/or lack of provider recognition of the concern for acetaminophen-induced hepatotoxicity.

Indeed, among patients with chronic liver disease, providing safe, effective pain management is complicated, as some of the mainstays, such as non-steroid anti-inflammatory medications and opioid analgesics are associated with hepatotoxicity.¹⁵ While

acetaminophen represents an appropriate treatment option, an average daily dose < 2gm is recommended.¹⁵ That HIV-infected individuals with evidence of advanced liver disease are only somewhat less likely to receive 2gm of acetaminophen is concerning. This was true using FIB-4 values and the individual components, AST, ALT and platelets, in a sensitivity analysis. Similarly, that HIV-monoinfected patients with an alcohol use disorder are more likely to receive 2gm of acetaminophen than those without an alcohol use disorder suggests that this population may be at increased risk for acetaminophen-induced liver toxicity.² That this relationship did not persist among HIV/HCV-coinfected patients suggests that providers treating patients with HIV/HCV-coinfection may be more cautious in their prescribing to this population.

This study should be interpreted in the context of limitations. The sample was predominantly male. We only capture medications received through the VA. Since patients may access acetaminophen elsewhere, our findings represent a conservative estimate of their acetaminophen exposure. We did not assess medication adherence. We relied on ICD-9 codes to capture diagnoses, such as alcohol use disorders, and may be underestimating their prevalence. We are unable to distinguish whether these diagnoses were active or treated. Further, our methods may underestimate the true prevalence of HCV infection.¹⁹

Acetaminophen receipt is common among HIV-infected patients despite risk factors for acetaminophen-induced liver injury. While it seems that clinicians were less likely to prescribe acetaminophen containing medications to HIV/HCV-coinfected patients, such prescriptions were not avoided in HIV-monoinfected patients despite evidence of advanced hepatic fibrosis and alcohol use disorders. Strategies, including electronic alerts and patient education, are needed to minimize exposure to these medications in patients in whom they may cause harm. Future studies examining acetaminophen and other potentially hepatotoxic medication prescribing in datasets covering multiple years and their association with hepatic fibrosis over time are warranted.

Acknowledgments

This work was generously supported by the Society of General Internal Medicine's Lawrence Linn Award, the Robert Wood Johnson Foundation Clinical Scholars Program, the Department of Veterans Affairs and the Veterans Aging Cohort study, funded by the National Institute on Alcohol Abuse and Alcoholism (U10 AA 13566).

This work was presented in an earlier version at the Veterans Aging Cohort Study Scientific Meeting, October 13th, 2011, Washington, D.C. and the Society of General Internal Medicine Annual Meeting, April 26th, 2013, Denver, CO.

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Take-Home Messages

- Despite their risk of acetaminophen-induced hepatotoxicity, acetaminophen is commonly prescribed to HIV-infected patients.
- Acetaminophen overuse (defined as ≥ 2 grams/day) is prescribed to HIV-infected patients regardless of evidence of advanced liver fibrosis.
- Though this may increase risk of acetaminophen-induced hepatotoxicity, the presence of HCV-coinfection and an alcohol use disorder were both associated with increased likelihood of acetaminophen overuse among HIV-infected patients.
- Strategies to promote safer acetaminophen prescribing to HIV-infected patients are warranted.

Figure 1a. Daily Acetaminophen Dose by FIB-4 >3.25 among HFV-monoinfected Patients

Figure 1b. Dairy Acetaminophen Dose by FIB-4>3.25 among HIV/HCV-coinfected Patients

Table 1
Factors associated with Acetaminophen Overuse (≥ 2 gm) compared to No Acetaminophen
among Patients Receiving Acetaminophen, N=14,885

Characteristic	Unadjusted	Adjusted (Full Model)	HIV+/HCV-, N=9436	HIV+/HCV+ N=5449
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
FIB4 > 3.25	0.97 (0.79, 1.18)	0.80 (0.65, 1.00)	0.83 (0.53, 1.28)	0.83 (0.66, 1.06)
age/10yrs		0.98 (0.92, 1.04)	1.02 (0.95, 1.10)	0.84 (0.74, 0.95)
Male		0.78 (0.56, 1.09)	1.08 (0.69, 1.69)	0.45 (0.27, 0.76)
Race/Ethnicity (ref: White)				
Black		0.91 (0.80, 1.03)	0.87 (0.74, 1.02)	1.01 (0.83, 1.24)
Hispanic		0.64 (0.50, 0.81)	0.70 (0.50, 0.97)	0.61 (0.42, 0.87)
Other		0.73 (0.54, 0.98)	0.71 (0.50, 1.00)	0.86 (0.47, 1.55)
Hepatitis C Virus		1.25 (1.11, 1.42)		
Alcohol Use Disorder		1.28 (1.08, 1.52)	1.56 (1.21, 2.02)	1.11 (0.89, 1.38)
Pain-Related Diagnosis				
Acute Pain-Related Diagnosis		3.39 (2.74, 4.20)	3.75 (2.84, 4.96)	2.90 (2.07, 4.05)
Chronic Pain-Related Diagnosis		4.00 (3.55, 4.51)	4.59 (3.93, 5.36)	3.30 (2.74, 3.99)