Combined effects of alcohol and hepatitis C: A secondary analysis of alcohol use biomarkers and high-risk behaviors from two medication trials for alcohol dependence ☆

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ABSTRACT

Objectives: The goal of this secondary analysis was to examine the combined effects of HCV infection and recent alcohol use on baseline biologic markers of alcohol consumption in two outpatient medication trials for alcohol dependence. In addition, the relationship between Hepatitis C virus (HCV) infection and behavioral risk factors for HCV infection in these clinical populations were examined.
Methods: Data ($n = 345$) from two randomized, placebo-controlled trials of naltrexone and psychosocial treatment for alcohol dependence (Study I, $n = 212$) and comorbid alcohol and cocaine dependence (Study II, $n = 133$) were used to examine baseline measures of HCV risk behaviors (injection drug use, needle sharing), and biomarkers of alcohol use (AST, ALT, GGT and CDT) were compared by HCV serostatus first within each study and then across studies.
Results: Although groups had differing sociodemographic profiles (as indicated by race, marital status, level of education) subjects in Study I exhibited no statistically significant differences from the Study II cohort in HCV prevalence (12.7 vs. 20.0%, $p = 0.07$), lifetime history of injection drug use (13.8 vs. 22.0%, $p = 0.74$), lifetime history of needle sharing (9.1 vs. 18.0%, $p = 0.62$). As such, the data from both studies were analyzed together. Regardless of drinking status, HCV infection was significantly associated with an upward shift in the baseline level of ALT, AST, and GGT ($p < 0.006$ for all measures) and a downward shift in baseline CDT ($p = 0.002$). When using standard laboratory cutoff values to determine clinically significant elevations, HCV seropositivity was significantly associated with elevations in ALT, AST, GGT ($p < 0.001$), and with decreases in CDT ($p = .002$).
Conclusions: These data emphasize the importance of evaluating HCV infection and HCV risk behaviors at intake in medication trials for alcohol dependence and also raise questions regarding the use of cutoff scores for ALT, AST, GGT and CDT levels as biologic markers of alcohol use in subjects when HCV status is unknown.

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1. Introduction

Hepatitis C is the most common blood-borne infection in the United States (Centers for Disease Control and Prevention, 1998). Estimates from the National Health and Examination Survey (NHANES III) report that the overall Hepatitis C (HCV) prevalence rate is 1.6% (approximately 4.1 million people) in the United States population (Armstrong et al., 2006). Approximately 74% (an estimated 2.7 million people) are chronically infected with Hepatitis C (Alter et al., 1999). Studies examining the prevalence of HCV among alcohol users have reported seroprevalence rates ranging from 14 to 36% (Bhattacharya & Shuhart, 2003). These studies provide valuable descriptions of the magnitude of HCV prevalence in alcoholics with clinically significant hepatic disease, but do not provide much information that is relevant to the alcoholic population typically encountered in clinical trials for alcoholism treatment.

Recently, interest has been focused on the prevalence of alcohol dependence among subjects with HCV. Such studies have shown that alcohol use exacerbates the progression of liver disease such as HCV (Zakhari & Li, 2007; Li, 2008; Anand et al., 2006). However, to date,

there are no reports describing the prevalence of hepatitis C or high-risk behaviors for hepatitis C (i.e. intravenous drug use, blood transfusions, multiple sexual partners, etc.) in subjects who participate in medication trials for alcohol dependence.

Within this area of clinical alcoholism research the potential combined effects of hepatitis C infection on biological markers of alcohol consumption has not been adequately explored. For most investigators, the use of routine HCV screening in clinical trials is cost prohibitive with the cost of a third generation HCV-EIA of approximately $60 (US) and $160 (US) for a confirmatory HCV RNA test (Carithers, Marquardt, & Gretch, 2000). However, without an understanding of the effects of undiagnosed hepatitis C infection on alcohol use biomarkers, accurate assessment of alcohol use in clinical trials becomes problematic.

The laboratory tests commonly used to monitor drinking status are alanine and aspartate aminotransferase (ALT and AST respectively), gamma glutamyl transpeptidase (GGT) and carbohydrate-deficient transferrin (CDT). Elevations in ALT and AST can reflect a wide array of hepatic and extrahepatic injuries unrelated to alcohol consumption (Limdi & Hyde, 2003). GGT and CDT are generally regarded as the laboratory markers most highly associated with heavy alcohol use. GGT can be elevated in 25–50% of alcohol dependent subjects seen in primary care settings and has a specificity of up to 89% for detection of heavy drinking in select populations (Conigrave, Saunders, & Whitfield, 1995). As with ALT and AST, GGT can also be elevated with hepatic disease. GGT elevations have been associated with advanced grade of hepatic inflammation and stage of fibrosis in persons with HCV (Noguchi et al., 1991; Silva et al., 2004).

Carbohydrate-deficient transferrin (CDT) is reported to have approximately 80% sensitivity and specificity for detecting alcohol consumption greater than 50–60 g/day (Rosman & Lieber, 1992; Sorvajarvi et al., 1996). In general, CDT and GGT have performed equally well as indicators of alcohol usage, with CDT being less influenced by underlying hepatic disease (Scouller et al., 2000). Since CDT has been utilized primarily as a marker for alcohol use, there is less information on CDT in non-alcoholic liver disease. Early work examining the effects of liver disease on CDT found that mild to moderate liver disease, even in the presence of hepatic fibrosis, had little effect on CDT levels (Stibler & Hultcrantz, 1987; Perret et al., 1997).

Although there is literature describing changes in transaminases and CDT in persons with Hepatitis C or chronic alcohol use, there are few papers reporting the potential combined effects of Hepatitis C and recent alcohol use on biomarkers for alcohol consumption. As is the case with reports of prevalence and high-risk behaviors, reports examining alcohol use biomarkers in persons with Hepatitis C are primarily drawn from populations with clinically significant liver disease or undergoing treatment for hepatitis C in these populations, elevations in serum transaminases and CDT correlated closely with recent alcohol use regardless of HCV status (Bell et al., 1993; Caldwell et al., 1995; Stauber et al., 1995; Perret et al., 1997). This relationship seems to hold for all but the most advanced liver disease in which hepatitis C infected individuals with end stage liver disease (Child-Pugh score >10) do have significantly higher elevations in CDT relative to other causes of liver disease regardless of alcohol use (DiMartini et al., 2001).

Although much can be inferred from existing literature examining HCV prevalence, risk and combined effects of HCV and alcohol use in the populations previously described, very little is actually known about the prevalence of HCV, and HCV risk behaviors in populations participating in outpatient clinical research trials for alcoholism. Even less is known about the potential combined effects of undiagnosed HCV and alcohol on biomarkers of alcohol consumption, which are commonly used to monitor drinking status in clinical trials.

Thus, the purpose of this analysis is to examine the prevalence of HCV and HCV risk behaviors and the potential combined effects of

HCV and alcohol on alcohol use biomarkers in a population typically encountered in medication trials for alcohol dependence.

2. Methods

2.1. Study sample

Subjects were participants in one of two randomized, placebo-controlled clinical trials of naltrexone for the treatment of alcohol dependence with and without co-occurring cocaine dependence. Study I (Oslin et al., 2008) included subjects with only alcohol dependence, while Study II (Pettinati et al., 2008) included subjects who were both alcohol and cocaine dependent.

As the present analyses focus solely on pretreatment laboratory measures, the clinical interventions and the outcome measures for the studies are not further described herein.

2.2. Assessment instruments

Research assistants who were not directly involved in the clinical care of subjects obtained risk and substance use assessments. Standard research assessments measured amount of drinking, severity of alcohol problems, and psychosocial functioning. The instruments included: 1) the Time Line Follow-Back (TLFB) (Sobell et al., 1988; Sobell & Sobell, 1992); 2) the Risk Assessment Battery (RAB); and 3) the Addiction Severity Index (ASI) (McLellan et al., 1980, 1992).

The TLFB is a semi-structured interview that uses a calendar format to record the quantity and frequency of drinking during a stated period of time. In this instance, drinking reports were recorded for the 30 days preceding detoxification, as well as during the treatment period. Quantity of alcohol was recorded in standard drinks (e.g., a 12-oz beer, a 5-oz glass of wine, or a 1.5-oz shot of hard liquor = one standard drink). For Study II, the TLFB was adapted to collect daily cocaine use, reported in dollar amounts used per day.

The RAB is an instrument used to measure high-risk behaviors for the transmission of HIV and other blood-borne diseases (Metzger et al., 1993). For both studies, the RAB was modified to ask questions about lifetime risk behaviors.

The ASI is a 1-hour, structured interview that measures the lifetime and recent (past 30 days) severity of problems in seven areas of biopsychosocial functioning: medical status, employment and self-support, alcohol use, drug use, legal status, family and social relationships, and psychiatric symptoms, as well as demographic information (McLellan et al., 1980, 1985).

All subjects received the following baseline laboratory studies prior to the start of study medication: Carbohydrate Deficient Transferrin (CDT), Chemzyme Panel/Bilirubin, and screening for Hepatitis C Antibody via enzyme-linked immunoassay (EIA) with western blot confirmation. Liver Function Tests (LFTs) were measured to assess hepatocellular injury that may be associated with the acute or chronic abuse of alcohol and other drugs. The LFTs included measures of ALT, AST and GGT (transaminase) values. CDT was measured by the Bio-Rad %CDT TIA (Carbohydrate Deficient Transferrin Turbidimetric Immunoassay).

Borrowing from previous descriptions of individuals infected with HCV without development of acute hepatitis, subjects with positive HCV tests without clinically significant hepatic illness are described as "subclinical" cases (Haley & Fischer, 2003).

2.3. Statistical analysis

Statistical analyses used SPSS Version 11.5 for Windows. Descriptive analyses included means and standard deviations for continuous variables and frequencies for categorical variables. Chi-square tests were conducted to investigate potential univariate associations between the study group demographic and clinical

factors (Table 1). Multivariable logistic regression analyses were conducted to evaluate the association between potential risk factors and hepatitis C seropositivity. The multivariate regression included age, gender, race, years of education and cocaine use in the models as covariates. Comparisons of mean values for ALT, AST, GGT and CDT were conducted to assess the relationship between the four biomarkers and HCV seropositivity, controlling for recent drinking behavior (Table 2). All analyses used two-tailed tests with the statistical significance set at alpha < 0.05.

Chi-square analyses were also conducted with biomarker groups defined as percentage above and below the standard lab cutoff value for each biomarker. Since there is variation in lab cutoff values over time, the lab measure was standardized by obtaining the raw cutoff value (determined by the central lab) and then transforming the measured lab (subject's lab value) value into the number of standard deviations above the central lab cutoff value. Lab values at or below the lab cutoff value were therefore defined as 0 (zero) and those one or more standard deviations above the cutoff were defined as 1 (one) and entered into a 2×2 table with HCV serostatus as the independent variable.

In order to accurately determine the associations between pretreatment drinking and the chosen biomarkers, we limited these analyses to participants whose biomarkers were measured within 10 days of presenting to treatment. This was done to limit the subacute recovery of liver enzymes seen after detoxification and to better reflect subjects' heavier drinking states prior to treatment entry. Analyses were controlled for number of heavy drinking days in the past 30. Heavy drinking was defined as five or more drinks in a single day for men, four or more for women. This criteria was based on other pharmacotherapy trials although both higher and lower levels of consumption could be considered clinically significant (Volpicelli et al., 1992; Anton, 1996; Kranzler & Van Kirk, 2001).

3. Results

Results are presented for two-hundred twelve (212) subjects from Study I and one-hundred thirty-three (133) subjects from Study II. The remaining subjects (twenty-eight from Study I and thirty-one from Study II) either had missing HCV data or had a gap of greater than 10 days between drinking data and measurements of LFTs and CDT.

Table 1
Subject demographics and clinical characteristics by study.

Subject demographics	Study I (n = 212)	Study II (n = 133)	Test statistic	p-value[a]
Age (years)	43.7 (10.7)	39.2 (6.9)	5.1	<0.0001
Gender (% male)	72.9	72.0	0.01	0.92
Race (% white)	72.9	21.3	101.8	<0.0001
Married (%)	38.7	17.3	20.0	<0.0001
Education (years)[b]	13.9 (2.7)	12.5 (1.9)	5.5	<0.0001
Clinical characteristics				95% CI
HCV seropositive (%)[b]	12.7	20.0	3.2	0.10
% Drinking days in last 30 days[c]	71.1 (27.3)	57.1 (26.6)	5.1	<0.0001 (8.7,19.4)
% Days heavy drinking in last 30 days[b]	60.8 (30.1)	49.9 (27.1)	3.8	<0.0001 (5.0, 16.6)
Ever used cocaine (%)[b]	26.9	100	202.9	<0.0001

[a] Continuity correction for binomial variables.
[b] Equal variances not assumed.
[c] Equal variances assumed.

Table 2
Comparison of mean alcohol use biomarker values and percentage above standard laboratory cutoff thresholds as a function of HCV serostatus and days of heavy drinking in the past 30.

Alcohol use biomarker	HCV positive (n = 41)		HCV negative (n = 247)	
ALT (mean value)	60.2		34.2	
ALT (% above threshold)	45.1		15.5	
AST (mean value)	46.0		31.3	
AST (% above threshold)	30.4		14.0	
GGT (mean value)	165.1		76.6	
GGT (% above threshold)	49.0		23.2	
CDT (mean value)	2.5		3.1	
CDT (% above threshold)	36.4		42.7	
Heavy drinking days median split	Low drink (n = 11)	High drink (n = 30)	Low drink (n = 122)	High drink (n = 125)
ALT (mean value)	43.9	49.1	**26.9**	**35.9**
ALT (% above threshold)	33.3	54.5	**11.1**	**20.6**
AST (mean value)	59.3	63.9	**26.6**	**42.3**
AST (% above threshold)	33.3	36.4	**9.6**	**19.1**
GGT (mean value)	151.5	183.3	**59.4**	**95.8**
GGT (% above threshold)	46.7	54.5	**15.8**	**31.1**
CDT (mean value)	2.5	2.5	**2.7**	**3.4**
CDT (% above threshold)	27.3	40.0	36.9	46.6

Groups in bold font are significantly different from each other ($ps < .006$).

3.1. Demographics and clinical characteristics

Subject demographics and clinical characteristics by study are presented in Table 1. There were no significant gender differences between the study groups, but there were significant differences in race, age, level of education and marital status between the groups. As compared to those in Study II, subjects in Study I were more likely to be Caucasian, (73.6% vs. 23.6%), older (44.1 vs. 38.7 years old), better educated (13.92 vs. 12.59 years) and more likely to be married (31.8% vs. 16.0%).

Among Study I (alcohol only) subjects, 12.7% were HCV positive, whereas in the Study II (alcohol and cocaine) population, 20.0% were HCV positive ($X^2 = 4.78$, $df = 1$, $p = 0.07$). The rates of HCV seropositivity approached, but did not achieve the level of statistical significance. Subjects in the two studies differed significantly in their lifetime history of cocaine use (26.9% vs. 100%, in Study II, $X^2 = 176.57$, $df = 1$, $p < 0.0001$), and percent days heavy drinking in the 30 days prior to entry into the study (61.8 vs. 49.6). However, subjects in the two studies did not differ significantly in percentage of drinking days or heavy drinking days in the 30 days prior to entering the study.

3.2. HCV risk behaviors by HCV serostatus by study

Multivariate logistic regression analyses examining the relationship between HCV risk behaviors and HCV serostatus, controlling for age, cocaine use, gender, race (white vs. non-white), study, and level of education confirm results from prior literature, which reports consistent, strong associations with injection drug use, needle sharing and HCV seropositivity (Wald = 55.3, OR = 33.9, $p < 0.0001$ for injection drug use and Wald = 45.3, OR = 24.5, $p < 0.0001$ for needle sharing). The number of lifetime sexual partners (>3 lifetime) and history of a blood transfusion did not significantly predict HCV seropositivity in this sample.

Results of the analysis of HCV risk behaviors by study controlling for age, cocaine use, gender, race (white vs. non-white), HCV serostatus, and level of education reveal that study group did not significantly predict engagement in the four major HCV risk behaviors, which were assessed (injection drug use, needle sharing, >3 sexual partners and blood transfusion). The percentage of lifetime IDU and needle sharing was high in both populations (13.8% vs. 22.0% for IDU and 9.1% and 18.0% for needle sharing) and not statistically significant between studies. Additionally, lifetime sexual partners and blood

transfusions were not significantly associated with study enrollment status.

The results of two comparisons describing the effect of HCV seropositivity on the four biomarkers used to monitor drinking behavior and liver function in this population are displayed in Table 2. Initially, the mean for each alcohol use biomarker (ALT, AST, GGT and CDT) was compared by HCV serostatus using standard two-tailed t-tests. In the case of the primary hepatic biomarkers (ALT, AST and GGT), HCV serostatus was highly associated with an upward shift in the mean level for each biomarker. Conversely, HCV seropositivity was associated with a significant downward shift in the mean baseline CDT ($p = 0.002$).

Drinking status (>16 heavy drinking days vs. <16 heavy drinking days in the past 30 days), had no effect on LFTs among HCV positive subjects. However, among HCV negative subjects, those with a greater number of heavy drinking days had significantly higher LFT values than did HCV negative subjects with fewer heavy drinking days ($ps < .006$) (Table 2).

The second comparison was conducted to determine if a clinically significant elevation existed between HCV serostatus and the four biomarkers when the standard laboratory cutoff value was used to determine "elevated" vs. "normal" lab values. The results of chi-square analysis of each biomarker by HCV serostatus are presented in Table 2. HCV seropositivity was significantly associated with the percentage of hepatic biomarkers (ALT, AST and GGT) above the lab threshold reference value. However, there was no association between HCV seropositivity and percentage of CDT above the lab threshold reference value.

Regarding heavy drinking status, HCV positive subjects again showed no differences in LFTs due to drinking status. Again, a significantly higher percentage of heavy drinking HCV negative subjects had values above the LFT thresholds than did those with less heavy drinking days.

4. Discussion

These data support four principal findings: 1) treatment seeking alcoholics without another active substance use disorder had high rates of HCV and high lifetime rates of injection drug use and needle sharing which were not significantly different from those of a treatment seeking population with comorbid cocaine and alcohol dependence, 2) regardless of recent drinking behavior, HCV infection in this population was associated with a significant upward shift in mean AST, ALT, and GGT values, 3) again, regardless of recent drinking behavior, this upward shift was also associated with elevations of AST, ALT and GGT above the standard lab cutoff value, and 4) although there was a paradoxical downward shift in mean CDT, CDT was the only alcohol use biomarker in this sample to remain within the lab cutoff range independent of HCV status.

What is perhaps most interesting in these findings is that regardless of drinking behavior, having HCV appears to lead to significantly higher ALT, AST and GGT lab values and significantly lower CDT values. In contrast, drinking behavior appears to elevate all LFTs in HCV negative subjects. This suggests that LFTs may be most useful as alcohol biomarkers primarily for those without HCV, as the presence of HCV appears to mask any potential variation in LFTs due to alcohol use. As hepatic injury or disease has been shown to elevate GGT (Silva et al., 2004), ALT and AST (Limdi & Hyde, 2003), it is possible that HCV infection leads to a ceiling effect for these LFTs such that alcohol use produces no further elevation beyond that produced by HCV.

As CDT is the biomarker that is least influenced by hepatic disease in alcoholics (Scouller et al., 2000), we would not expect to see much impact of HCV on CDT in this study. In fact, supporting the extant literature, CDT levels did not appear elevated in relation to HCV status in our outpatient cohort. CDT in fact was significantly decreased in our HCV seropositive cohort. Despite our attempt to capture our sample in

a pre-acute recovery stage, the fact that CDT was not elevated above the standard laboratory cutoff in our sample is consistent with prior reports of rapid decline in CDT levels in as little as 8 days after cessation of drinking (Bell et al., 1993).

As mentioned earlier in this paper, observational studies have found consistent associations with alcohol and HCV transmission. The cause for this is multifactorial, but alcohol's known psychological effects (i.e. disinhibition, loss of judgment, mood elevation or depression), can lead to engagement in high-risk sexual and drug taking behaviors.

Although previously cited observational studies find that alcohol is an independent risk factor for HCV infection, it is obvious that alcohol use per se is not a mode of transmission of HCV. What can be inferred however is that alcohol use, especially chronic, heavy alcohol use, may be associated with isolated high-risk behaviors in certain populations, which in turn increase the risk for HCV infection.

At the time a drinker, usually in their fourth or fifth decade of life, comes in for treatment of primary alcoholism, high-risk behaviors associated with HCV transmission may have occurred as isolated or infrequent incidents in the remote past (i.e. experimental IDU or sexual promiscuity during early adulthood). It seems unlikely that subjects will report such behavior at the time of entry into treatment for alcoholism, as such events are temporally remote from the current treatment episode, and are of a highly sensitive nature.

Our data are consistent with prior literature reporting that alcoholic cohorts have a high prevalence of HCV infection and engage in high-risk behavior for transmission of blood-borne infections (Avins et al., 1994; Boscarino et al., 1995; Stein et al., 2000; Malow et al., 2001). In particular, IDU and needle sharing are quite common in our Philadelphia study populations. Previous studies have reported increased rates of IDU in alcoholics with HCV, but our data may offer additional insights into this problem as we were able to compare our treatment seeking alcoholic population to a lower functioning, treatment seeking alcohol and cocaine dependent population. The lack of a significant difference in overall prevalence of HCV and HCV risk behaviors between these two populations that seem disparate on the surface suggests that alcohol dependent individuals seeking outpatient treatment may, in fact, be at the same high risk for HCV infection as subjects with both cocaine and alcohol dependence.

Although sexual promiscuity and blood transfusions have been identified as primary routes of transmission for HCV, our analysis did not show them as independent risk factors in our population. This is most likely due to limitations in our assessment of these behaviors. There is no standard risk threshold for HCV transmission from sexual activity, but CDC has reported increased risk for HCV in persons with ten to fifty or more lifetime sexual partners (Centers for Disease Control and Prevention, 1998; Alter et al., 1999). The version of the RAB we used did not have items allowing for precise quantification of lifetime sexual partners, thus we were not able to obtain a measure of sexual behavior consistent with the threshold reported by CDC.

In regard to blood transfusions, the RAB did not assess the frequency or year in which the subject received a blood transfusion. The studies reported here did screen out individuals with serious medical conditions, which would require multiple blood transfusions (i.e. hemophilia or renal dialysis). Since the blood supply in the United States has been effectively screened for HCV since the early 1990s, any person receiving a blood transfusion over the last 14 years is unlikely to have contracted HCV via this route. Our study therefore likely screened out those individuals at highest risk for transfusion-borne HCV.

There are five main limitations for the findings from this study. First, these data were taken from two clinical trials of pharma-cotherapies for alcohol (Study I) and combined alcohol and cocaine dependence (Study II). Such trials have strict inclusion/exclusion criteria which exclude individuals such as those with other substance dependence (e.g., opioids), as well as those with serious or unstable medical or psychiatric disorders. As such, these findings are most

relevant to other medication trials similar to these, but less relevant to the population of alcohol or alcohol and cocaine dependent individuals as a whole.

Second, as HCV status was established only by HCV-EIA without confirmatory HCV RNA testing, it is possible that a proportion of the subjects with HCV positive serostatus had mounted an immune response to the HCV infection, and thus were currently disease free. Although such RNA analyses are costly, it is important that future studies examine HCV seropositive subjects both with and without active disease to further establish the impact of HCV on alcohol use biomarkers.

Third, fifty-nine subjects or roughly 14% were excluded from the analysis due to missing data or falling outside the ten-day acute phase recovery window. However, the missing data was proportional in each study group.

Fourth, we only examined baseline data, which eliminates our ability to examine any impact that HCV status may have on alcohol biomarkers during treatment for alcohol dependence. As such alcohol biomarkers are used in both standard outpatient treatment and clinical research settings to monitor alcohol use (Allen & Litten, 2001; Anton, Lieber, & Tabakoff, 2002), it is important to determine what impact HCV serostatus has on these biomarkers during periods of abstinence and alcohol use. Finally, these studies did not specifically assess factors such as nutritional status or other liver disease, which could potentially confound the relationship between HCV serostatus and alcohol use biomarkers. As such, additional studies that assess nutrition, as well as other liver diseases would add substantially to the study of the impact of HCV on alcohol biomarkers.

Our results suggest that undiagnosed HCV infection is significantly associated with elevated transaminase levels. Interpretation of these biomarkers when HCV status is unknown could therefore be skewed in the direction of over-reporting alcohol use or alcohol-related hepatic inflammation, especially when relying on lab cutoff values of AST, ALT and GGT.

The data presented here draw attention to the need for HCV risk assessment in medication trials for alcohol dependence in which AST, ALT, GGT and CDT will be used as markers of alcohol consumption. As routine screening for HCV at time of study entry may be impractical, detailed HCV risk assessment could provide a cost conscious guide for determining when screening for HCV is most appropriate.

Contributors

Author A (JGP) developed and drafted the manuscript. Author B (CFT) developed the initial concept for the study and conducted the preliminary data analyses, aided by Author C (HMP). Author A, in conjunction with authors D (KMK), E (JRV) and F (DWO) expanded the aims and conducted additional analyses. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

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