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REVIEW

Alcohol use disorder and its impact on chronic hepatitis C virus and human immunodeficiency virus infections

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Abstract

Alcohol use disorder (AUD) and hepatitis C virus (HCV) infection frequently co-occur. AUD is associated with greater exposure to HCV infection, increased HCV infection persistence, and more extensive liver damage due to interactions between AUD and HCV on immune responses, cytotoxicity, and oxidative stress. Although AUD and HCV infection are associated with increased morbidity and mortality, HCV antiviral therapy is less commonly prescribed in individuals with both conditions. AUD is also common in human immunodeficiency virus (HIV) infection, which negatively impacts proper HIV care and adherence to antiretroviral therapy, and liver disease. In addition, AUD and HCV infection are also frequent within a proportion of patients with HIV infection, which negatively impacts liver disease. This review summarizes the current knowledge regarding pathological interactions of AUD with hepatitis C infection, HIV infection, and HCV/HIV co-infection, as well as relating to AUD treatment interventions in these individuals.

Key words: Hepatitis C virus; Human immunodeficiency virus; Hepatitis C virus/human immunodeficiency virus co-infection; Liver; Alcohol

Core tip: The present review is focused on alcohol use disorder and hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infection, as well as HCV/

HIV co-infection.

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INTRODUCTION

Alcohol abuse is a major cause of preventable liver disease worldwide, and alcohol use disorder (AUD) is associated with substantial disease burden in western countries[1]. According to 5th edition of the Diagnostic and Statistical Manual of Mental Disorders[2], AUD encompasses both alcohol abuse and alcohol dependence. Table 1 presents the diagnostic criteria for AUD and other definitions of unhealthy alcohol use, such as the recommendations of the United States National Institute on Alcohol Abuse and Alcoholism.

In the United States, almost 9% of the adult population meets the AUD criteria and alcohol contributes to 79000 deaths annually[3]. Within the European Union, alcohol misuse causes 14% of deaths in men and nearly 8% of deaths in women, with alcohol-related mortality disproportionally impacting young people[4]. In Spain, unhealthy alcohol use is exhibited by 5% of the population between 15 and 64 years old, and 15% report at least one binge drinking episode within the prior year[5]. Moreover, the pattern of binge drinking is becoming increasingly prevalent, mainly among young individuals.

Per capita alcohol consumption is strongly correlated with liver cirrhosis mortality rates globally[6]. However, the short- and long-term impacts of binge drinking with regards to the development and severity of alcoholic liver disease (ALD) are not yet known. Per capita alcohol consumption is strongly correlated with liver cirrhosis mortality rates across countries[5]. Notably, the medical literature reveals wide heterogeneity in the methods used to assess alcohol exposure, and it can be challenging to analyze time-varying exposures like alcohol consumption over time[7].

Epidemiology of AUD in hepatitis C virus and human immunodeficiency virus infection

Addressing alcohol use is critical in the management of hepatitis C virus (HCV)-infected patients, as AUD is associated with poor clinical outcomes and liver-related deaths in this patient group[8]. Compared to the general population, HCV-infected adults tend to consume greater amounts of ethanol[9], being over twice as likely to consume more than one alcoholic drink per day (34% *vs* 14%) and almost 8 times more likely to consume over three drinks per day (19% *vs* 2%)[10].

Moreover, alcohol abuse is associated with concomitant use of illegal substances, and 30% to 50% of patients with a history of substance abuse consume alcohol[11]. This is highly important since 2/3 of new HCV infections in the western world are associated with drug injection[12]. Accordingly, the prevalence of HCV infection is higher among patients with AUD who are current or past injecting drug users[13]. Within a cohort of patients with AUD admitted for hospital detoxification in the Barcelona area, HCV prevalence was as high as 20%[14]. However, other researchers in Spain reported a much lower prevalence of 3.5%[13], possibly due to differences in patient selection.

The prevalence of HCV infection is confounded by the degree of liver disease. Cross-sectional studies performed in hepatology clinics showed that HCV prevalence was higher among patients with advanced liver fibrosis, and almost universal among HCV-infected patients with hepatocellular carcinoma[15,16]. On the other hand, HCV prevalence ranged from 1% to 10% in community-oriented studies of individuals with AUD but without clinically apparent liver disease[17,18]. A recent meta-analysis including 24 studies reported that the average weighted prevalence of HCV infection among patients with AUD was 16.3%[13].

AUD may also be common among human immunodeficiency virus (HIV)/AIDS patients, with a prevalence ranging from 30% to 50%[19]. High prevalences of alcohol consumption have been reported in HIV/AIDS cohort studies from the United States[20,21], Europe[22-24], South Africa[25], and other parts of the world[26]. In the Women's Interagency HIV Study, 14%-24% of female HIV/AIDS participants reported hazardous alcohol use within the past year[27]. On the other hand, patients with AUD show a lower prevalence of HIV infection than HCV infection[14], which is confounded by prevalence of injection drug use.

AUD AND CHRONIC HCV INFECTION

Effect of alcohol on HCV replication

Alcohol metabolites apparently enhance viral protein expression as well as the heterogeneity of HCV quasispecies[28]. Some authors describe RNA-HCV increases among patients who use alcohol[29]. However, a meta-analysis performed by Anand *et al*[30] in 2005 showed no association between RNA-HCV and alcohol consumption.

Impact of alcohol on HCV infection persistence

Spontaneous resolution of HCV infection requires an early and wide immune response against HCV viral proteins[31]. Once acute HCV infection is controlled, the presence of memory T-cell populations is associated with reduced persistence of infection in re-exposed individuals[32]. HCV infection persistence is also associated with loss of specific T-cell proliferation, and reduced migration of effector T cells to the liver[33]. HCV-infected patients with AUD show functional impairment of dendritic cells[34], which partly explains the association between alcohol use

Table 1 Diagnostic criteria for alcohol use disorder and other definitions of unhealthy alcohol use

AUD (DSM-5)
In the past year[2], have you[1]
Had times when you ended up drinking more, or longer than you intended?
More than once wanted to cut down or stop drinking, or tried to, but couldn't?
Spent a lot of time drinking? Or being sick or getting over the aftereffects?
Experienced craving - a strong need, or urge, to drink?
Found that drinking or being sick from drinking often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
Continued to drink even though it was causing trouble with your family or friends?
Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, irritability, anxiety, depression, restlessness, nausea, or sweating? Or sensed things that were not there?
Risky alcohol use[178]
Drinking more than the recommended amount by the National Institute on Alcohol Abuse and Alcoholism
> 14 drinks per week of > 4 drinks on any day for men
> 7 drinks per week or > 3 drinks on any day for women or men > 65 yr
Problem drinking
Use of alcohol accompanied by alcohol-related consequences but not meeting criteria for AUD

[1]Meeting any two of the 11 criteria during the same 12-mo period is consistent with AUD. The severity of an AUD-mild, moderate, or severe-is based on the number of criteria met. AUD: Alcohol use disorder; DSM-5: Diagnostic and statistical manual of mental disorders.

and lower odds of spontaneous HCV resolution[35,36].

Effect of alcohol on HCV-related immunity

Mice that are chronically exposed to ethanol exhibit diminished immune responses to HCV-core protein, mainly due to impaired maturation of dendritic cells[34]. In HCV-infected patients, dendritic cells present impaired allostimulation capacity, which is more apparent in the presence of alcohol[34]. Alcohol and HCV infection exert synergistic effects, suppressing major histocompatibility complex class Ⅱ[37] *via* functional impairment of the proteasome (intracellular protein complexes that degrade unnecessary or damaged proteins) and alterations in interferon signaling[38]. This could partly explain the lower efficacy of interferon-based HCV treatment regimens among patients with AUD[39].

Effect of alcohol on cytotoxicity

Enhanced hepatocyte apoptosis is observed in HCV infection, which is apparently associated with impaired immune responses rather than directly attributable to the viral infection[40]. Hepatocyte apoptosis is mediated by cytotoxic T cells and natural killer cells *via* caspase activity[40]. BCL-2 protein is associated with mitochondrial permeability, and its expression is reduced in HCV-infected hepatocytes[41]. Alcohol seems to enhance hepatocyte apoptosis through down-regulation of BCL-2 expression[40].

Alcohol and oxidative stress

The HCV core viral protein is associated with higher oxidative stress. It binds the mitochondrial wall, facilitating calcium entrance, electron transport, and increased reactive oxygen species, which results in increased oxidative stress that damages the cell[42]. This protein also targets microsomal triglyceride transfer protein activity, thus modifying hepatic very-low-density lipoprotein particle assembly and secretion, which leads to liver steatosis[43]. Moreover, the HCV core viral protein alters the oxidant/antioxidant state of the liver in the absence of inflammation, consequently producing mitochondrial DNA damage[44].

In HCV-core transgenic mice, chronic ethanol administration is associated with higher lipid peroxidation and synergic induction of TGF-β1 and hepatic stellate cells[45]. The HCV-core protein cooperates with ethanol to activate some p38 mitogen-activated protein kinase pathways, resulting in polygene modulation, and contributing to liver disease pathogenesis[46]. In alcohol-fed NS5A transgenic mice, the synergistic effect between HCV infection and alcohol is dependent on mechanisms involving Toll-like receptor 4, which belongs to the innate immune system[47]. Alcohol consumption and HCV infection impact FOXO3 expression, thus impairing antioxidant capacity in the liver[48].

In humans, indirect evidence suggests that oxidative stress is associated with more extensive liver injury in patients with AUD and HCV infection, as they tend to show higher serum levels of malondialdehyde (a lipid peroxidation product), poor glutathione peroxidase activity, and stimulation of Th1 response cytokines[49]. Moreover, patients with AUD present major lipid peroxidation, and the loss of antioxidant capacity is associated with liver fibrosis[50]. Among HCV-infected patients who drink alcohol, liver fibrosis is independently associated with liver steatosis, oxidative stress, age, and iron

deposits in the liver[51].

Alcohol and progression of HCV-related liver disease

Alcohol consumption is associated with more extensive progression of HCV-related liver damage[52,53]. No safe level of alcohol consumption has been described, as even HCV-infected patients who drink moderate amounts of alcohol (30 g/d) experience progressive liver fibrosis[54-56]. A meta-analysis assessed 20 studies that were published between 1995 and 2004, and found that the relative risk of progression to liver cirrhosis or decompensated liver disease among HCV-infected patients was 2.3 times higher, with a 95%CI of 1.7-3.3, among those who drank alcohol compared to abstainers[52]. However, the majority of included studies were performed in liver units, and thus might be biased towards patients with more severe forms of liver disease[52]. Alcohol consumption is also associated with higher risks of cirrhosis decompensation and liver-related death[57]. Moreover, alcohol consumption has a synergistic effect with chronic hepatitis C, increasing the risk of liver cancer[58].

Assessment of liver disease in patients with AUD and HCV infection

In both HCV infection and ALD, liver fibrosis is the main prognostic factor of liver disease progression[59,60]. Although liver biopsy is the gold standard for liver fibrosis assessment[61], it is associated with several rare complications and is not usually performed in patients with substance use disorders[62]. Recent reports describe the estimation of liver fibrosis using several non-invasive biological markers derived from laboratory parameters routinely used in clinical practice, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count.

Of these potential markers, FIB-4[63] and the aspartate aminotransferase/platelet ratio index (APRI)[64] have been validated against the gold standard of liver biopsy in HCV-monoinfected patients as well as HCV/HIV-coinfected patients[65-68]. These markers perform better for detecting either the absence of liver fibrosis or the presence of advanced liver fibrosis[63,64]. However, clinical experience using these markers in patients with AUD is limited[69], and concerns have been raised about the possibility of overestimating liver fibrosis in patients with alcoholic steatohepatitis. Moreover, ALD is a formal contraindication for the use of Pohl's score[70]-an index that uses aminotransferase levels and platelet count. Transient elastography has also been used to assess liver fibrosis in ALD[71], but the presence of severe liver steatosis may distort results, leading to overestimation of advanced liver fibrosis[72].

In prior studies, we have defined alcohol-related liver disease (ARLD) as the presence of any two of the following criteria: Elevated AST to between 74 and 300 U/L, AST/ALT $\geqslant$ 2, and total bilirubin > 1.2 mg/dL[73,74]. Within a cohort of AUD patients admitted for hospital detoxification in metropolitan Barcelona, Spain, 14.6% met those criteria, and ARLD was associated with mid-term mortality[75].

Impact of HCV infection on hospitalizations and mortality of patients with AUD

As previously mentioned, alcohol use is associated with worse prognosis in HCV-related liver disease. It is estimated that 36% of liver cirrhosis among HCV-infected individuals is attributable to alcohol use[76]. HCV infection also has a deleterious impact on clinical outcomes among patients with AUD[77-80]. Tsui *et al*[77] identified 6354 AUD-related hospital admissions, and reported that the HCV-positive patients were twice as likely to die (4.4% *vs* 2.4%, $P < 0.01$), and showed significantly longer hospital stays (19% longer, 95%CI: 12%-27%). Another study included patients from the United States Nationwide Inpatient Sample Dataset who had a primary or a secondary discharge diagnosis of alcoholic hepatitis, and reported that HCV-positive patients had higher mortality with an odds ratio (OR) of 1.29 (95%CI: 1.12-1.49, $P < 0.01$)[78].

Patients with AUD who are exposed to HCV infection probably differ from those who are not exposed with regards to co-morbidities or behaviors associated with poorer survival, such as the use of illicit drugs[81]. However, even in studies that have accounted for various lifestyle factors, HCV infection remains associated with both overall mortality, showing a hazard ratio (HR) of 2.55 (95%CI: 1.50-4.33, $P < 0.01$), and liver-related mortality (HR = 3.24, 95%CI: 1.18-8.94, $P = 0.02$)[79].

In our study of 675 AUD patients admitted for hospital detoxification, we examined the impact of HCV infection on mortality. Our results showed that HCV infection was associated with higher mortality, and that this effect was more apparent in patients with younger ages at admission (HR = 3.1, 95%CI: 1.3-7.3, $P < 0.01$) and those who were co-infected with HCV/HIV (HR = 3.9, 95%CI: 2.1-7.1, $P < 0.01$)[80]. In the same Barcelona cohort, we recently reported that AUD patients with HCV mono-infection showed an increased risk of liver-related death in comparison to AUD patients without HCV-infection (HR = 3.92, 95%CI: 2.03-7.59)[82].

Interferon-based treatment of HCV infection in patients with AUD

In the era of HCV antiviral therapy including interferon, infection treatment was challenging in individuals who consumed alcohol[8]. In fact, alcohol use was a major reason for a lack of HCV treatment[83,84]. Several researchers analyzed strategies to extend HCV treatment to patients with unhealthy alcohol use. Le Lan *et al*[85] performed an observational study of HCV treatment in alcohol-drinking patients, in which drinking in moderation was encouraged but not required. Of the study population, 30% continuously abstained, 34% consumed low-risk amounts of alcohol, and 36% continued to drink risky amounts. The overall sustained viral response (SVR) rate was 48% with no difference observed between

Table 2 Treatment interventions for unhealthy alcohol use and alcohol use disorder

Condition	Intervention
Unhealthy alcohol use	Brief intervention
	Motivational interviewing
AUD	Hospital detoxification
	Individual and group therapy
	Approved pharmacological treatments:
	Disulfiram
	Acamprosate
	Naltrexone
	Nalmefene
	Investigational treatments:
	Baclofene
	Topiramate
	Gabapentin

AUD: Alcohol use disorder.

abstainers and low-risk drinkers[85], confirming prior results in a Swiss HCV cohort[86].

Evon *et al*[87] performed a randomized clinical trial in the United States, which included 9-mo intervention comprising counseling, case management, and motivational interviewing for patients ineligible for HCV treatment (31% due to alcohol abuse). The intervention was associated with a 2.38 relative risk of being deemed eligible (95%CI: 1.21-4.68). The groups did not differ with regards to the proportion of patients that eventually received HCV antiviral therapy[87].

Interferon-free treatment of HCV infection in patients with AUD

The advent of direct-acting antivirals and interferon-free regimens has dramatically changed the landscape of HCV treatment, with most registration trials and pilot real-life experiences reporting SVR rates of over 90%[88]. Although treatment is now more feasible for patients with substance use disorders[89,90], to date, very few patients with AUD have been included in clinical trials[91-93].

The current American Association for the Study of Liver Diseases - Infectious Diseases of America guidelines for HCV treatment advocate abstinence from alcohol[94]. When appropriate, these guidelines suggest interventions to facilitate the cessation of alcohol consumption, ranging from brief interventions for patients with low alcohol intake[94], to referral to mutual help groups and specialty treatment for patients with established AUD[94]. While alcohol consumption is not a formal contraindication for HCV treatment, a year of abstinence from alcohol is thought to be necessary to achieve adequate treatment adherence[95].

There remains a need for a change in the provision of HCV treatment such that patients with AUD and HCV infection can benefit from viral eradication. Expansion of the capacity of primary care clinics or addiction clinics to provide HCV treatment has been successfully tested in several areas of the United States[96] and Australia[90]. These experiences should be replicated worldwide to more effectively treat difficult-to-reach populations[97].

AUD treatment in patients with HCV infection

Brief interventions involving feedback and discussion of the negative consequences of alcohol abuse are efficacious at motivating reduced alcohol consumption among among patients with unhealthy alcohol use[98], but not patients with alcohol dependence. Such brief interventions can be targeted towards patients with HCV infection, with delivery at the primary care level or in hepatology clinics[94,99]. More intensive treatments, such as motivational enhancement therapy, can also reduce the number of drinking days among patients with chronic HCV infection[100]. Other type of interventions, such as group therapy, can reportedly motivate abstinence from alcohol in 44% of patients in an HCV clinic[101].

Table 2 summarizes the various treatment strategies for patients with AUD. Specialty treatment should be favored in such cases, and patients should be offered detoxification; specific pharmacotherapy including disulfiram, acamprosate, naltrexone, or nalmefene; and psychosocial support[3]. Some researchers have reported satisfactory results with baclofene in patients with overt end-stage liver disease[102].

AUD AND HIV INFECTION

Effect of alcohol on the immune system

The combined effects of alcohol and HIV on the immune system have been investigated in simian models[103]. Alcohol and HIV infection show a synergistic impact on gastrointestinal tract integrity, causing initial depletion of intestinal CD4 cells[104,105]. Loss of intestinal wall integrity is associated with increased permeability, microbial translocation, and immune activation[106]. Immune activation is crucial for HIV disease progression[107], and is reportedly a better predictor of disease progression than HIV viral load[106,108]. While alcohol seems to impact the adaptive immune responses to HIV infection in animal models, the results in humans are mixed[103]. In a study of HIV-infected patients, blood alcohol levels relative to alcohol intake were higher before antiretroviral treatment compared to after treatment[109].

Alcohol and HIV disease progression

Prior to widespread use of antiretroviral therapy (ART), epidemiological data suggested that alcohol use was not associated with HIV disease progression[110,111]. However, following the advent of ART, several authors have reported reduced ART effectiveness among patients with AUD[19,112]. In 2003, Samet *et al*[113] investigated a cohort of HIV-infected patients, and reported cross-sectional data suggesting that alcohol consumption negatively impacted HIV disease progression. Alcohol consumption was associated with lower CD4 cell counts and higher HIV viral loads in patients receiving ART. A later longitudinal study of the same cohort demonstrated that heavy alcohol use in patients not receiving ART was

associated with lower CD4 cell counts but not with HIV viral load[114].

Chander *et al*[115] at John Hopkins University reported that heavy alcohol consumption was associated with reduced viral suppression of HIV infection and lower treatment adherence. Wu *et al*[116] investigated 325 subjects receiving ART and found that, after adjusting for adherence, daily drinkers showed a nearly four-fold increase in the odds of detectable HIV viral load. This association was non-significant for regular drinkers. Their results further showed that alcohol use was not associated with CD4 cell count, and that alcohol consumption was not associated with HIV viral load among patients not receiving ART[116]. On the other hand, Baum *et al*[117] investigated HIV-infected patients receiving ART, and reported that alcohol use was associated with lower CD4 cell counts, greater risk of showing a CD4 cell count of < 200, and an increased HIV viral load over time.

More recent studies indicate that the benefits of ART seem to outweigh the detrimental effects of alcohol use, reinforcing the importance of initiating ART and ensuring adequate treatment adherence[118]. A study in a Swiss HIV cohort revealed no effect of alcohol consumption on either virological failure or CD4 cell count, both among ART-receiving and ART-naïve patients[119]. That study also demonstrated that heavy drinkers were more likely to interrupt ART; however, only 2.8% of participants were heavy drinkers[119]. A recent French study of HIV/AIDS patients reported that low levels of alcohol consumption (< 10 g/d) were associated with higher CD4 counts compared to in abstainers[120]. However, the beneficial effects of such low levels of alcohol consumption may be confounded by other healthier behaviors exhibited by moderate drinkers[121].

Overall, evidence acquired during the first decade of ART use suggested that AUD may impact HIV disease progression; however, more recent studies do not support those findings. These contradictory results may be partly explained by poor adherence to treatment and barriers to proper medical care associated with AUD.

Alcohol and comorbidities

Alcohol use is associated with unprotected sex and syringe sharing, thus elevating the risks of HIV acquisition and transmission[122-124]. Moreover, alcohol use is associated with higher prevalence of depressive symptoms[125], which can influence ART initiation[126], treatment adherence[127], treatment discontinuation[128], and disease progression[129,130]. Other substance use disorders frequently co-exist in patients who exhibit alcohol abuse[11], which is also associated with poorer treatment adherence, reduced HIV viral suppression, and lower retention in care[112,131].

Heavy alcohol use is related to liver disease among patients with HIV infection[132,133], and is also associated with cardiovascular disease[134] and exacerbations of chronic obstructive pulmonary disease[135]. A systematic review of 13 studies reported that heavy alcohol use was associated with elevated risk of cardiovascular disease, with a risk ratio of 1.78 (95%CI: 1.09-2.93)[134].

Alcohol and mortality in HIV infection

Alcohol is commonly regarded as an underappreciated modifiable risk factor in individuals with HIV infection, with or without HCV co-infection[116]. A retrospective study from northern California evaluated data from between 1996 and 2005, and found that higher mortality rates were associated with diagnosis of a substance use disorder (alcohol only, drug only, or alcohol and drug)[136]. In the HIV-LIVE cohort of HIV-positive patients with alcohol problems, short-term mortality was associated with homelessness and drug use[137], and long-term mortality was associated with HCV infection and high levels of inflammation markers[79,138]. A study from the VACS cohort revealed that even non-hazardous levels of alcohol consumption were associated with decreased survival[139]. Recent data from the same VACS cohort shows that among HIV-positive participants, alcohol use was associated with greater physiological injury. Moreover, within this cohort, a greater risk of mortality was associated with an Alcohol Use Disorders Identification Test value of $\geqslant$ 4 drinks/mo (HR = 1.25, 95%CI: 1.09-1.44), and of $\geqslant$ 30 drinks/mo (HR = 1.30, 95%CI: 1.14-1.50)[140].

HIV treatment in patients with AUD

Alcohol use co-existing with other substance use is associated with lower quality of HIV care[141] and poor retention in care[131]. A systematic review of 53 studies published between 2010 and 2015 showed that 77% of studies revealed that alcohol use was negatively associated with the HIV treatment cascade, *i.e.,* access to care, ART prescription, and treatment adherence[142]. This suggests that unhealthy alcohol use should be targeted to increase the proportion of HIV/AIDS patients who achieve viral suppression.

Even modest alcohol consumption has been associated with poor ART adherence[139]. Hendershot *et al*[143] performed a meta-analysis of 40 studies, and showed that patients who drank relatively more were 50%-60% less likely to adhere to ART compared with those who abstained or drank relatively less. Alcohol consumption appears to be dose-dependently related to ART adherence[115], and shows a temporal relationship to missed ART treatments[144].

AUD treatment in HIV-infected patients

Among HIV/AIDS patients who drink alcohol, brief interventions are reportedly efficacious for reducing the frequency of alcohol use and the frequency of unprotected sex[145,146]. However, patients abusing alcohol might need more intensive treatment. Some authors report that the addition of motivational interviewing[147] and problem solving therapy may be necessary to improve ART adherence[148]. An intervention called retention through enhanced personal contact has also been tested to improve retention among HIV-positive patients with alcohol use or mental illness[149].

Table 3 Non-invasive methods for analyzing liver fibrosis in patients with alcohol use disorder, hepatitis C virus infection and hepatitis C virus - human immunodeficiency virus co-infection

Ref.	Setting	Non-invasive method	Method for detecting alcohol consumption	Finding
Lieber *et al*[69]	VA studies (2) of alcoholic liver disease	APRI[1]	Average alcohol intake	Low sensitivity and specificity of APRI in comparison to liver biopsy, especially in subjects with HCV
Chaudhry *et al*[169]	HIV Hopkins clinical cohort	APRI	Past 6-mo hazardous drinking	No effect of alcohol on APRI values in HCV/HIV co-infection
Blackard *et al*[170]	WIHS cohort	FIB-4[2]	Recent drinking	No association between alcohol intake and FIB-4 values in HCV/HIV co-infection
Muga *et al*[171]	AUD patients admitted for detoxification	FIB-4	Past 6-mo unhealthy drinking	No association between FIB-4 and alcohol use in HCV/HIV co-infection
Fuster *et al*[173]	HIV-live cohort	FIB-4 and APRI	LDH	No association between LDH and liver fibrosis measured with FIB-4 or APRI
Lim *et al*[174]	VACS cohort	FIB-4	AUDIT-C[3]	Advanced liver fibrosis correlated with alcohol use

[1]APRI: AST to platelet ratio index= {[AST/AST upper limit of normal (IU/L)]/platelet count (10^9/L)} × 100[64]; [2]FIB-4 = age × AST (IU/L)/platelet count (10^9/L) × ALT (IU/L)$^{1/2}$[63]; [3]AUDIT-C: Alcohol Use Disorders Identification Test[179]. HIV: Human immunodeficiency virus; AUD: Alcohol use disorder; APRI: Aminotransferase/platelet ratio index; HCV: Hepatitis C virus; LDH: Lifetime drinking history; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; VA: United States Department of Veteran Affairs; WIHS: Women's Interagency HIV study; VACS: Veterans Aging Cohort study.

Chander *et al*[150] recently performed a cross-sectional survey among HIV care providers, and found that although the majority reported that they usually screen for alcohol use, only 10% used a formal screening tool. Moreover, knowledge of pharmacotherapy for AUD was low, and most care providers referred patients to outside resources for treatment[150].

AUD AND HCV/HIV CO-INFECTION

A proportion of patients with both AUD and HCV infection also have HIV infection. In fact, HCV/HIV co-infection is clinically relevant among individuals with history of injection drug use[151]. HIV infection is associated with faster progression of HCV-related liver fibrosis[152,153] as well as earlier occurrence of decompensated liver disease[154,155], liver cancer[156], and liver-related death[157]. During the interferon era, co-infection with HIV compromised HCV treatment response[158,159]. However, interferon-free regimens have greatly increased the efficacy of HCV antiviral treatment among co-infected patients, both in clinical trials[160] and in real-life scenarios[161,162]. On the other hand, HCV infection is associated with increased risk of ART-related liver toxicity[163], which is even higher with concurrent alcohol use[164]. In cases of HCV/HIV co-infection, alcohol use is also associated with poorer treatment adherence[165], and seems to increase HCV RNA levels[166,167].

Until recently, the impact of alcohol use on HCV-related liver disease in HIV-infected patients had not received much attention in the literature. Older studies suggest that alcohol use is associated with biopsy-proven liver fibrosis in cases of co-infection[152,168]. However, studies using non-invasive methods have produced mixed results, highlighting the shortcomings of non-invasive methods-including methods relying on ALT, AST, and platelets-in patients with ALD[70,69]. Table 3 summarizes the different studies that have used non-invasive methods to evaluate liver fibrosis in patients with AUD and HCV infection or HCV/HIV co-infection.

A cross-sectional study in an urban HIV/AIDS cohort revealed that heavy alcohol use was associated with advanced liver fibrosis measured using the APRI score[169]. However, when the patients were stratified by HCV infection, high APRI score was associated with hazardous alcohol use only among patients without HCV infection[169]. Blackard *et al*[170] investigated a cohort of women, and demonstrated that alcohol use was not associated with FIB-4 values among HCV/HIV co-infected patients. Within our cohort of AUD patients, FIB-4 was significantly higher among HCV/HIV co-infected patients compared to in HCV monoinfected patients[171]. In the HIV-LIVE cohort, lifetime alcohol consumption[172] was not associated with the absence of liver fibrosis (FIB-4 < 1.45), and similar results were found for the presence of advanced liver fibrosis (FIB-4 ⩾ 3.25) and among patients with HCV infection[173]. A study in the VACS cohort-which included a larger number of patients and a different measure of alcohol consumption-reported greater risks of advanced liver fibrosis (measured based on FIB-4) among co-infected patients who exhibited nonhazardous drinking (OR = 14.2, 95%CI: 5.91-34.0) or hazardous/binge drinking (OR = 18.9, 95%CI: 7.98-44.8), or who had alcohol-related diagnoses (OR = 25.2, 95%CI: 10.6-59.7) relative to uninfected individuals who were nonhazardous drinkers[174]. The somewhat discordant results among studies may be partly due to differences in the methods used to describe alcohol use and other characteristics of the study population[169-174].

French researchers investigating HCV/HIV co-infected patients recently found that advanced liver fibrosis (measured with transient elastography) was more common among those with an alcohol-related diagnosis (OR = 3.06, 95%CI: 1.42-6.60) compared

to non-hazardous drinkers[175]. Elastography may be more reliable than laboratory markers for assessing liver fibrosis in HCV/HIV co-infected patients with AUD. Additionally, the combination of HCV infection and alcohol use is associated with greater mortality within HIV/AIDS cohorts[79,176], highlighting the need to further address alcohol use in co-infection. Although it can be challenging, it is feasible to reduce alcohol use in the setting of HCV/HIV co-infection[177].

CONCLUSION

To reduce the impact of HCV, HIV and ethanol on liver disease, patients with AUD should be screened for HCV and HIV infection, and interventions should focus on both reducing alcohol consumption and treating viral infections. Moreover, patients with HCV infection or HCV/HIV co-infection should be screened for unhealthy alcohol use to prevent end-stage liver disease. Several treatment interventions are efficacious for reducing alcohol consumption among individuals with HCV infection or HCV/HIV co-infection.

In settings where AUD often coexists with other substance use and viral co-infections, higher levels of co-morbidities are expected. Health care facilities for treatment interventions and multidisciplinary approaches must be widely accessible for managing AUD and associated diseases.

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