**Review**

**HIV and the Liver**

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Among individuals with HIV infection, liver disease remains an important cause of morbidity and mortality, even with the availability of agents that cure hepatitis C infection and suppress hepatitis B replication. The causes of liver disease are multifaceted and continue to evolve as the population ages and new etiologies arise. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis and hepatitis viruses such as A, D, and E have emerged even as hepatitis C has receded. Newer antiretroviral agents may increase risk of weight gain and subsequent fatty infiltration, and prior use of nucleotide-based therapies may continue to impact liver health. Several barriers including economics, social stigma, and psychiatric disease impact identification of liver disease, as well as management and treatment interventions. Hepatocellular carcinoma is emerging as a more common and late-diagnosed complication in those with HIV infection and liver disease.

**Keywords**: HIV, hepatitis, NAFLD, NASH, ART, liver, antiretroviral therapy, hepatocellular carcinoma

**Introduction**

Over the last 2 decades we have gained a growing appreciation of the central role of liver disease in the course and outcomes of those with HIV infection. During this time we have witnessed a clear evolution with regard to the leading causes of liver disease and the management of those processes in individuals with HIV infection. The introduction of effective antiretroviral therapy (ART) in 1996 opened the door to longer life expectancies that permitted the expression of the full natural history of various liver diseases, often with an accelerated course compared with immunocompetent individuals. An early focus on hepatitis B virus (HBV) infection and drug-associated liver toxicity was quickly overshadowed by the emergence of our understanding of the importance of hepatitis C virus (HCV) infection on liver disease progression to cirrhosis and liver cancer. The development of direct acting agents with the ability to eradicate HCV infection in most individuals including those with HIV infection led many to believe that liver disease was no longer a substantial clinical issue in the setting of HIV infection. However, liver disease continues to be a major component of morbidity and mortality in those with HIV infection. HBV infection has re-emerged as an important contributor to liver disease. Although alcoholic and nonalcoholic fatty liver has become a leading cause of liver transplantation in immunocompetent persons, we have barely scratched the surface in terms of understanding the unique epidemiologic and biologic patterns and processes that contribute to fatty liver disease among immunosuppressed patients. Viral infections that were long minimized in terms of their importance such as hepatitis A, D, and E now appear to be important contributors to progressive liver disease in some populations.

Since 2006, the US National Institutes of Health and industry partners have supported a biennial symposium designed to provide input from various stakeholders, including those representing hepatology, infectious diseases, pharmacology, alcohol and drug abuse, and government regulatory bodies. The most recent iteration of this meeting was held in September 2018 in Moran, Wyoming. In an effort to define the cutting edge of knowledge within the field, experts from a variety of domains were challenged to provide up-to-date information in their topic area regarding issues central to the research agenda of the future. In this report we summarize the key findings of the meeting in an effort to provide a roadmap for the next several years of research in the area of HIV and liver disease.

**Changing HIV Epidemiology**

The last decade has witnessed major changes in the epidemiology and management of HIV infection in the United States and elsewhere. Overall rates of new HIV infection declined between 2008 and 2013, and the introduction of preexposure prophylaxis (PrEP) has helped to stabilize the incidence at under 40,000 new cases/year in the United States. New infections of HIV are highly concentrated in the southeastern United States (52%) as well as in small urban geographic pockets and East Coast and West Coast cities. Men who have sex with men (MSM) account for 68% of risk for new infection. On a proportionate basis, the highest risk of infection is among people of color including African-American men and women and Hispanic men. Added to this mix are now discrete outbreaks of HIV infection primarily associated with injection drug use among young people with opioid use disorder. This pattern of spread is best characterized by the outbreak in Scott County Indiana, a rural, mostly white population where multigenerational sharing of drug paraphernalia led to an epidemic...
Viral Hepatitis

Hepatitis A. In 2016, an outbreak of hepatitis A virus (HAV) infection was first described in the San Diego Metropolitan area. This epidemic was primarily associated with poor sanitation among homeless populations who had not previously been vaccinated or exposed to hepatitis A virus (HAV). The transient nature of this population led to rapid spread with secondary epidemics occurring in numerous other cities. According to the CDC, since the new HAV infection outbreaks were first observed in 2016, more than 15,000 cases, 8500 (57%) hospitalizations, and 140 deaths due to HAV infection have been reported (Figure 1). Simultaneously, reports of acute HAV infection among MSM populations increased in urban populations in Europe and the United States. Many of those with HAV infection had HIV infection. Reports at this meeting and elsewhere suggest that a large portion of the population with HIV infection is either unvaccinated or has lost detectable antibody. Indeed, overall HAV vaccine coverage in the general population is abysmal with rates of under 10% reported for adults who are older than 19 years of age in the United States. However, vaccination or revaccination among individuals with HIV infection does appear to yield protective antibody response in more than 90% of those treated. Modeling studies demonstrate that herd immunity does not occur until antibody levels reach at least 70%. However, following an outbreak of HAV infection in France, MSM still appeared to have substantial infection risk despite achieving at least 70% antibody seroprevalence. Protective antibody titers following vaccination appear to be lower than in those who recover from natural HAV infection. The severity of acute liver disease among those with HIV infection appears to be high (ie, higher rates of coagulopathy) and anecdotal data suggests that a rare relapsing form of HAV infection may be more common.

Hepatitis B and D. The importance of HBV infection in the setting of HIV infection has been continuously underestimated and overshadowed relative to concerns about HCV infection since the mid-1990s. Despite this oversight, the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) study clearly demonstrates the importance of HBV infection as a contributor to overall morbidity and mortality in individuals with HIV infection. Similarly, a detailed analysis of patient outcomes in the Veterans Administration system also identifies hepatitis B as a major contributor to liver injury. Despite a plethora of guidelines that suggest that all patients with HIV infection be tested for HBV and appropriately vaccinated if not currently infected or previously exposed, many patients remain unprotected. Despite widespread use of ART active against HBV there appears to be continued unawareness of the presence of chronic HBV infection or the risk of new HBV infection in those with HIV infection.

There is increasing interest in the simplification of ART regimens, particularly in those that have had viral control on a triple drug-therapy regimen for several years. Simplification often involves reduction to a 2-drug regimen and a combination of dolutegravir with rilpivirine, and abacavir or lamivudine has been studied in clinical trials with some success. However, those studies excluded patients with chronic HBV infection. Failure to recognize previously suppressed HBV infection with transition to a regimen that does not have activity against HBV will lead to flares of hepatitis that can be severe or even fatal in those with preexisting hepatic fibrosis. There are anecdotal reports of simplification with removal of tenofovir leaving lamivudine or emtricitabine as the only hepatitis B active agent. Patients with chronic HBV infection who are on such a regimen are at high risk of the emergence of resistant virus with HBV breakthrough due to failures.
the presence of tyrosine-methionine-aspartic acid-aspartic acid (YMDD) motif mutations. The use of vaccine for prevention remains underappreciated. Even when HBV vaccination is administered, it is often ineffective (Figure 2). Systematic reviews of vaccine responsiveness yield a wide range of results with protective efficacy defined as greater than 10 million IU/mL occurring in 20% to 70% of vaccine recipients.15 Several studies have examined vaccination strategies to try and improve response rates.18-21

Hepatitis D virus (HDV) infection occurs as either a superinfection or coinfection with HBV infection. In Europe the frequency of HDV among patients with HBV/HIV coinfection is relatively high. A EuroSIDA collaboration reported that 14.5% of patients with HIV infection and chronic HBV infection were anti-HDV positive.22 Indeed, screening guidelines call for routine testing for HDV among all HBV-surface antigen-positive patients. In the United States the frequency of HDV infection is lower and routine testing has not been performed. Epidemiologic studies in Northern California have suggested that rates of as high as 8% may be seen in individuals with chronic HBV infection.23 However, exceedingly low rates of screening and lack of availability of HDV RNA testing probably lead to marked underestimation of the disease burden.24 Studies from Spain and elsewhere suggest that HDV/HBV/HIV coinfection is associated with more rapid progression of liver disease and increased rates of hepatocellular carcinoma (HCC).25

Hepatitis C. The overall prevalence of HCV infection among individuals with HIV infection has been well-established for several years. In many HIV cohorts in the United States and Europe, a blended composite antibody prevalence of 20% to 25% has been described (Figure 3).

Though guidelines have suggested HCV testing in all individuals with HIV infection since 1999, HCV screening and surveillance is suboptimal. A recent study in Italy in those who were newly diagnosed with HIV infection found that 58% were unaware that they also had HCV infection.26 People who inject drugs have fragmented care and do not have substantial political voices. Many jurisdictions lack resources to measure burden by surveillance because HCV research is underfunded. In many states, systems are designed to restrict access to HCV direct-acting antivirals (DAAs) for people who inject drugs including restrictions on sobriety, fibrosis presence, and specialist access. This is in spite of evidence that 1) people who inject drugs respond equally well to HCV therapy with excellent adherence;27,28 2) high coverage of needle syringe programs and opioid substitution therapy reduces the incidence of HCV transmission by 74%,29 and 3) treatment without restrictions on HCV can markedly decrease prevalence of HCV.30 Reinfections can occur and both treatment and harm reduction strategies are essential to control HCV transmission and treatment as prevention can markedly decrease new HCV infections.31-33 Presence of HCV RNA is highly associated with progression of fibrotic disease leading to cirrhosis and liver cancer. Many, though not all, studies suggest that HIV suppression significantly reduces rates of hepatic fibrosis but does not eliminate hepatic decompensation among those advanced disease.34,35 The availability of all-oral DAA regimens that were tolerable and highly efficacious among those with HIV infection opened the door to eradication efforts in the HIV-infected population. Although carefully conducted clinical trials suggest that there is no difference in overall treatment response compared to individuals without HIV infection, some, though not all, real-world studies continue to describe some decrement in sustained viral response rates or improvement in health-related quality of life.36-38 Effective therapy appears to halt injury and fibrotic progression and reduce the risk of HCC. The epidemiologic linkage between exposure to HCV and HIV in areas most affected by the opioid epidemic appears to be substantial, with HCV infection typically occurring first, followed by later introduction of HIV infection into closed population groups. Modeling data suggests that a combination of needle exchange services, opioid substitution therapy, and other addiction services combined with active treatment of HCV infection represents the best approach to blunt this epidemic.39 Other modalities may be needed in high-risk MSM populations.

Hepatitis E. The prevalence and significance of hepatitis E virus (HEV) infection among individuals with HIV infection remains controversial. In the United States, rates of exposure among those with HIV infection appear to be similar or perhaps slightly higher than the age-specific prevalence in the general population.40 Rates of exposure to this zoonotic disease primarily representing genotype 3 infection are high in both the immunocompetent and HIV-infected populations in some regions of Spain and France.41,42 Persistent chronic infections are reported more frequently in those areas that
have been observed in the United States in HIV-infected and in immunosuppressed solid organ transplant populations. It is possible that underreporting of HEV infection is a common phenomenon. The causes of this are multifactorial and include low rates of testing, lack of availability of testing facilities, lack of US Food and Drug Administration (FDA) approved assays, and possibly immunosuppression-associated seroconversion failure or seroreversion. Loss of antibody was observed in 40% of HIV-infected solid organ transplant recipients. Overall prevalence of HEV infection in the United States appears to be decreasing, which may be related to changes in behavioral patterns including increased use of processed meats and decreased direct animal exposure by the general population in recent decades. In contrast, some population groups in southern Europe continue to consume high levels of cold smoked sausage derived from pig liver (figatella), which appears to harbor a high risk of acute HEV infection.

Fatty Liver

As HCV infection recedes in importance due to the availability of curative therapies, fatty liver disease in all of its forms and manifestations has become recognized as an increasingly important etiology of liver disease in individuals with HIV infection. Fatty liver disease can be broadly divided into alcoholic and nonalcoholic steatosis. Steatosis associated with alcohol use is a direct and expected outcome of alcohol oxidation within the liver. The amount of alcohol necessary to cause steatosis and the consequences of persistent steatosis with inflammation and oxidative injury (alcohol-associated liver disease) is not clearly defined. If one defines hazardous drinking behavior as greater than 14 drink equivalents per week for men and half that for a woman, then 10% of study participants in the Johns Hopkins HIV Clinical cohort of 6000 adults with HIV infection met that definition.

Clinical trials in patients with nonalcoholic steatohepatitis (NASH) often exclude subjects having more than 21 drinks per week for men or 14 drinks per week for women, but in the individual patient it is difficult to define the exact amount of alcohol consumption that may be associated with liver injury due to hepatic steatosis. Gene polymorphisms such as PNPLA3, overall nutritional status, and oxidative stress from other etiologies may all contribute to individual responses. Patients with HIV infection are more likely to have metabolic syndrome than those without HIV infection, even if they do not have higher body mass index. When alcohol is not implicated as the causative etiology, the presence of steatosis in the liver implies the presence of nonalcoholic fatty liver disease (NAFLD). A subset of individuals with this condition have NASH, which is associated with progressive fibrosis leading to cirrhosis. In the setting of HIV infection, the exact prevalence of NAFLD and NASH remain uncertain. This is due in part to variation in the modalities used to define the presence of liver disease. Most commonly, fatty

![Figure 3. Worldwide prevalence of hepatitis C virus (HCV)/HIV coinfection](image-url)
Hepatocellular Carcinoma

Over the last decade, HCC prevalence has increased among those with HIV infection. In a US Veteran’s Administration cohort of 24,000 individuals with HIV infection, the year 2003 represented a nadir with increased HCC rates observed in most subsequent years (Figure 4). Most of this was associated with HCV/HIV coinfection. Prevalence increases of 11%/year have been described in a multicohort consolidated analysis. HCC risk was associated with lower CD4+ count but not CD4+ count nadir. Interestingly, control of HIV replication does not seem to substantially reduce risk of cancer development.

Mechanisms of Liver Injury

HIV infection is associated with an increased risk of cirrhosis in individuals with chronic HCV and HBV infections, alcohol-related hepatitis, and possibly NAFLD. The risk of liver disease in individuals with HIV infection may be higher due to greater exposure to hepatotoxins such as alcohol and some older ART drugs. In addition, there are numerous mechanisms through which HIV could potentiate liver disease pathogenesis, including 1) direct effects of HIV on hepatocytes, stellate cells, or Kupffer cells; 2) increasing translocation of an altered gut microbiome into portal blood; or 3) depletion of CD4+ lymphocytes and widespread derangement of other immune responses. Although relevant animal models are lacking, in vitro studies have already revealed key insights into how HIV might potentiate the pathogenesis of HCV infection.

HCV infects hepatocytes where reactive oxygen species (ROS) accumulate and upregulate transcription of transforming growth factor beta-1 (TGFβ1) through a nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway. TGFβ1 stimulates stellate cells to produce the extracellular matrix that accumulates in cirrhosis. HIV cannot infect hepatocytes. However, the HIV envelope interacts with hepatocytes promoting ROS accumulation, and HIV may infect hepatic stellate cells. Both interactions potentiate the pro-fibrogenic pathways, enhancing TGFβ1 production in hepatocytes and production of the extracellular matrix by stellate cells. Although this model was originally established in immortalized hepatocyte or stellate cell lines, the Chung lab confirmed that HIV accentuates the profibrogenic effects of HCV using a more physiologic model coculturing hepatocytes (Huh 7.5.1 cells) and stellate cells (LX2).

Hepatic macrophages (Kupffer cells) also contribute to the pathogenesis of liver disease. HIV directs Kupffer cells and may disrupt Kupffer cell number or function. When activated, macrophages may stimulate stellate cells to produce extracellular matrix, a process that is represented by release of soluble CD163. HIV and HCV infection are each associated with elevated CD163 compared to controls, and levels are highest in individuals with HIV/HCV coinfection. CD163 levels correlate with hepatic inflammation and fibrosis in individuals with HIV/HCV coinfection.

HIV infection is associated with increased translocation of microbial bacteria. Since nearly all portal blood drains through the liver, increased microbial translocation may alter the pathogenesis of liver disease either qualitatively (if the microbial components differ) or quantitatively (if there is more net translocation) to the liver. Several studies have reported a different intestinal microbiome in

Figure 4. Prevalence of hepatocellular carcinoma (HCC) in the United States in individuals with HIV infection. (Used with permission from John Wiley and Sons). Solid lines represent actual prevalence. Dotted lines represent prevalence adjusted by direct standardization to age distribution of entire population from all calendar years.
individuals with HIV infection.\textsuperscript{73-75} However, at least some differences do appear to be confounded by alterations in the microbiome of MSM who are enriched in the HIV study population compared with heterosexual men and women versus being due to HIV infection itself.\textsuperscript{76}

Without regard for qualitative differences in the microbial contents, it is also possible that greater net translocation of bacteria promotes liver fibrogenesis.\textsuperscript{72} The association of HIV infection with elevated levels of blood correlates of microbial translocation like lipopolysaccharide or of Kupffer cell activation such as CD163 and soluble CD14 support that hypothesis.\textsuperscript{70,72,77} Further work is needed to clarify if there are consistent disruptions in the intestinal microbiome linked to HIV, if a “more favorable” microbiome can be established, and if that favorable microbiome alters disease phenotypes.

HIV infection may also affect HCV and HBV-induced chronic liver disease by altering immunity. Individuals with HIV infection have chronic immune activation and altered type 1 interferon responses.\textsuperscript{78-80} Compared with persons with HIV infection alone, the CD8+ T cells from individuals with HIV/HCV coinfection are less potent and are more likely to express markers of exhaustion such as PD1 and CD39.\textsuperscript{84} PD-L1 levels appear to be present at higher levels in coinfection than in those with HCV monoinfection.\textsuperscript{82} Differences in the B cells and natural killer (NK) T cells of individuals with HIV/HCV coinfection have also been described.\textsuperscript{83,84}

Although there is comparatively more research on the pathogenesis of HIV-related liver disease in persons with chronic HCV infection, it is likely that some mechanisms contribute to other forms of liver disease. For example, increased microbial translocation, increases in hepatocyte ROS, and alterations in Kupffer cell physiology are mechanisms by which alcohol may promote liver fibrosis and steatosis (and are accentuated by HIV).\textsuperscript{85} Likewise, HIV-associated altered antiviral immunity would be expected to affect both HBV and HCV infections.

### Treatment and Barriers to Treatment of HBV and HCV

There are substantial barriers to treatment of HBV and HCV infections, including low recognition of a largely silent disease as well as social and structural issues. Both viruses infrequently cause symptomatic disease so people do not seek medical care. Persons with HBV and HCV infections may suffer from stigma further precluding them from accessing care. Transmission is usually silent. Most people are asymptomatic or minimally symptomatic for years or decades. When they do access care, testing may not be performed or may be insufficient. The effects of fatigue and diminished quality of life may be attributed to other factors.

Men and women are equally represented in the acute HCV infection epidemic and many women only access care during pregnancy. Pregnancy is an opportunity to test and potentially treat in the third trimester. A recent small study showed a 100% sustained virologic response (SVR) rate without adverse fetal or maternal outcomes.\textsuperscript{86}

Individuals with HIV/HCV coinfection achieve the same rates of SVR as individuals with HCV monoinfection. The major concern with people with coinfection is drug-drug interactions that include some ART and common drugs such as statins and proton pump inhibitors. Before choosing an HCV regimen, careful assessment of current medications with potential HCV therapy is required using a pharmacist or online resources (www.hep-druginteractions.org; https://www.hcvguidelines.org/unique-populations/hiv-hcv).

HBV treatment in individuals with HIV infection is recommended for all patients with HIV/HBV coinfeciton, regardless of CD4+ cell count or need for HBV treatment. (https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arp/25/hbv-hiv) ART must include 2 drugs active against HBV, preferably tenofovir and emtricitabine, regardless of the level of HBV DNA. Such a regimen will reduce the likelihood of immune reconstitution inflammatory syndrome against HBV and reduce the risk of viral resistance that could occur with newer regimens without HBV active drugs or with lamivudine or emtricitabine alone. Treatment interruptions should be avoided as they can lead to serious life-threatening flares in HBV. Options to treat HBV alone are limited to interferons as all nucleos(t)ides have HIV activity. ART containing tenofovir-based therapy has been shown to prevent new HBV infection, in individuals with HIV infection for whom HBV infection failed.\textsuperscript{87}

### Management of Alcohol and Drug Use and Psychiatric Disorders in HIV

Drug and alcohol dependence, often associated with mental illness, are important comorbidities that affect treatment outcomes and influence disease epidemiology and transmission. It is well established that mental illness increases risk of HIV infection and in a reciprocal manner, HIV increases risk for and severity of mental illnesses. Although HIV care practitioners can address many of their patients’ medically oriented health issues, they often have limited expertise in management of psychiatric disorders, which increase visit time and may overwhelm resources. Lyketsos and colleagues reported that 54% of patients entering an HIV primary care clinic setting had Axis I diagnoses including major depression (20%), adjustment disorder (18%), and cognitive impairment (18%) and that 74% were diagnosed with substance use disorder.\textsuperscript{88} Presence of depression was associated with discontinuation of ART, which led to decreased survival.\textsuperscript{89} Schizophrenia and bipolar disorders are also increased in those with HIV infection. HIV care practitioners can play a major role in HIV-infected with substance use populations disorders by 1) treating depression; 2) advocating for patient care in drug-treatment centers and 3) accepting that relapse is part of the disease process. Integrated care settings appear to provide better overall management of those with depression.\textsuperscript{90}

Substance disorder occurs in a complex overlay of social, psychiatric, and
economic issues. For individuals with HIV infection who have coinfections with viral hepatitis, access to care can sometimes be difficult. As noted, many states restrict access of HCV DAAs for people who inject drugs. There are sobriety restrictions including marijuana use, for which there is no evidence that use affects treatment outcomes. Many jurisdictions have fibrosis restrictions, but those at the greatest risk of transmission often have low levels of hepatic fibrosis. A few insurers still mandate “one and done” policies that allow only one treatment for a disease with a relatively low but real reinfection risk rate. Current guidance (www.hcvguidelines.org) from the American Association for the Study of Liver Disease and Infectious Diseases Society of America suggest at least annual HCV RNA testing for people who inject drugs after HCV clearance (either spontaneous or through treatment).

Simmons and colleagues provided evidence that individuals with HCV/HIV coinfection were at higher risk of reinfection and recurrence than other groups.101 Opioid agonist therapy has been shown to reduce incidence of HCV infection among people who inject drugs.102 Combined with needle syringe exchange programs, even greater reduction in transmission can be demonstrated.103 Even active injectors can be successfully treated for HCV infection.104

Unhealthy alcohol use is another important cofactor in modulation of liver disease among individuals with HIV infection. It influences provision of HIV care, sexual risk behaviors, medical comorbidities, and mental health.105,106 Overall all-cause mortality among individuals with HIV infection is higher than in those without HCV infection in all categories of alcohol use/month (Figure 5). Despite this, alcohol use is not prioritized as a problem by either patients or health care practitioners, and few HIV practitioners report implementation of evidence-based alcohol-related care in their practices.107 Various modalities are available to modulate unhealthy alcohol use including medications (acamprosate, disulfiram, naltrexone) and counseling interventions (Motivational Enhancement Therapy, Cognitive Behavioral Therapy). In one study, drinking outcome measures were improved among women with HIV infection in just one series of 20-minute face-to-face intervention sessions.108 Similar results were reported by Kahler et al, using one 60-minute interview with follow-up phone calls and “booster” sessions.109 Adjunctive use of medications like naltrexone has been shown to be safe and effective in those with HIV infection.110,111

Research Agenda: The Path Forward

Despite advances in the last several years, many key questions remain to be addressed. With regard to HIV care, underserved, and unidentified populations remain difficult to access. Research into identifying and integrating these populations into care (implementation research) remains a crucial need. This has been highlighted by guidance from the CDC, National Institute of Allergy and Infectious Diseases, and US Department of Health and Human Services.112 Although ART regimens have evolved such that direct hepatic toxicity is reduced, concern regarding long-term and persistent effects of prior nucleoside-based therapies on the liver remains. Research into effects of exposure on hepatoportal sclerosis and development of portal hypertension will be important. This may be one factor into the observation that decompensation occurs at higher rates in those with HIV and liver disease even when underlying processes (eg, HCV infection) are treated. The mechanisms that underlie the observations remain to be elucidated. As our population with HIV infection ages, HCC occurrence is increasingly frequent and important. Are there optimal screening and surveillance strategies in those with HIV infection that differ from those without? Does risk remain in those with controlled (suppressed) HIV infection? There are few data regarding aging and the liver itself in the context of HIV infection. New pathways for liver injury and fibrosis continue to be identified. What role do immune defects that persist after HIV suppression play in these? It appears that the role of chemokines and chemokine blockade is emerging as an important feature of fibrosis. Much focus is on patients with NASH but there may be a role for chemokine receptor 5 (CCR5) blockade in those with abnormal liver tests without clear etiology for the liver disease. The microbiome remains largely unexplored within the HIV-infected population. Can it be manipulated? Indeed, do those with HIV infection differ from those not infected? Hepatic fibrosis remains the key endpoint for many disease pathways. Are there new markers of fibrosis and regression of fibrosis that need to be explored (eg, kynurenine)? With regard to HBV/HIV coinfection, prevention and cure remain elusive. Prevention is largely reliant on successful vaccination but outcomes are suboptimal in individuals with HIV infection. The reasons for this remain unknown. In a practical sense new strategies are needed to improve HBV vaccine outcomes. These may include use of toll-like receptor 9 (TLR9) or other agonists. With regard to functional cure, covalently closed circular (ccc) DNA clearance is essential. Experts remain divided on whether antiviral or immune approaches (or both) are needed. New biomarkers of cure are also needed and exploration of novel biomarkers like pre-genomic RNA have not yet been described in HIV-infected cohorts. Curing HBV infection prevents an emergence of HDV, but since that

Figure 5. Alcohol and HIV infection: mortality rates per 100 person-years by total drinks per month and by HIV infection status.105 (Used with permission from Elsevier Ireland Ltd Publishers).
will be difficult, better screening, new drugs, and new targets are needed. We do not know why HCC risk is increased when HDV infection is present in the setting of triple infection (HBV/HDV/HIV). Though many believe that HCV infection is no longer a problem because it can be cured, many questions remain. What are the long-term effects of cure on hepatic fibrosis and HCC, as well as non-liver morbidities in those with HIV? Do recreational drugs affect DAA metabolism and effectiveness in real-world settings? Would long-term DAs serve as PrEP in high-risk populations? Can we treat subgroups for even short durations? Does a vaccine make sense? If yes, how, who and when? NAFLD/NASH appears to be on the rise in those with HIV infection and the population in general in the United States and elsewhere. Is there more steatosis in individuals with HIV infection? What factors related to HIV infection impact disease severity and progression? Do we need modification of non-invasive biomarkers in the context of HIV infection and its treatment? Will studies of new therapeutic agents enter the HIV-infected population? Liver and kidney transplantation in HIV are effective modalities but immunologic effects of protease inhibitors on rejection have raised questions. Is there an expanded sense? If yes, how, who and when?

Financial affiliations in the past 12 months: Dr Sherman has received grant support or contracts awarded to his institution from AbbVie, Gilead Sciences, Inc, Intercept Pharmaceuticals, Inc. MedImmune, and Merck & Co, Inc. and served as an advisor or consultant to UniQure and Inovio Pharmaceuticals; and served on data and safety monitoring boards for Watermark and Medpace. Dr Peters has served as an advisor to Abbott. Her spouse is employed by Hoffman-La Roche. Dr Thomas has no relevant financial affiliations to disclose.

Funding for this conference was made possible [in part] by the National Institutes of Health under Award Number 2R13AI071925-08. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the US Government. Also supported in part by educational grants from: Abbott Diagnostics, Dova Pharmaceuticals, Gilead Sciences, Inc., Janssen Therapeutics, LP, Salix, and ViIV Healthcare.

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