Published in final edited form as:

Hepatology. 2014 January ; 59(1): . doi:10.1002/hep.26638.

Human Immunodeficiency Virus and Liver Disease Forum 2012

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Abstract

In the U.S. more than 1.1 million individuals are infected with the human immunodeficiency virus (HIV). These patients exhibit a high frequency of coinfections with other hepatotropic viruses and ongoing fibrosis leading to cirrhosis and liver-related mortality. The etiologies of liver disease include viral hepatitis coinfections, drug-related hepatotoxicity, fatty liver disease, and direct and indirect effects from HIV infection including increased bacterial translocation, immune activation, and presence of soluble proteins that modulate the hepatic cytokine environment. New treatments for HCV using direct acting agents appear viable, though issues related to intrinsic toxicities and drug:drug interactions remain. Recent research suggests that acute HCV infection, unrecognized hepatitis D infection, and hepatitis E may all represent emergent areas of concern. Antiretroviral agents, including those used in past years may represent risk factors for hepatic injury and portal hypertension. Key issues in the future include systematic implementation of liver disease management and new treatment in HIV-infected populations with concomitant injection drug use, alcohol use, and low socioeconomic status.

Keywords

HIV; HCV; HBV; HCC; Injury; Pathogenesis; Treatment; Epidemiology

Introduction

Despite significant progress in our understanding of liver disease in patients infected with the human immunodeficiency virus (HIV), progressive hepatic fibrosis leading to portal hypertension, and the development of hepatocellular carcinoma continue to represent significant etiologies of morbidity and mortality. Hepatologists are frequently asked to provide care and guidance to patients and health care providers regarding optimal management of liver-related comorbidities. These include viral hepatitis A through E, drug-related hepatotoxicities, and emerging processes such as non-cirrhotic portal hypertension. (1) Many HIV care providers have a limited understanding of the complexities associated with the management of liver disease. Similarly, many hepatologists are uncomfortable addressing the nuanced relationship between use of appropriate antiretroviral therapies and treatment of hepatitis B and C. To reduce this barrier to care, a multidisciplinary conference

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designed to bring together cross-disciplinary expertise in Hepatology, Infectious Diseases, Epidemiology, Regulatory Affairs, Drug Development, and Behavioral Sciences was convened.

The 4th Biennial Forum on HIV and Liver Disease was held in Jackson, Wyoming in September 2012. Support was provided by three Institutes of the National Institutes of Health (National Institute of Allergy and Infectious Diseases, National Institute of Alcohol Abuse and Alcoholism, and the National Institute of Drug Abuse). Several pharmaceutical industry sponsors also provided unrestricted grants to the University of Cincinnati Continuing Medical Education Office, who provided oversight in accordance with ACCME guidelines to ensure rigorous and unbiased presentation of data under discussion. The primary purpose of the Forum was to define the current state-of-the-art with regard to key issues related to liver injury and liver disease in the setting of HIV infection, and to identify key research questions in the field. A summary of the prior HIV and Liver Disease conference was published in HEPATOLOGY. This publication seeks to update the progress made in the interim two year interval and to redirect the research agenda priorities.

Epidemiology/Natural History (Brooks, Soriano, Fontana, Goodman)

Since the advent of combination antiretroviral therapies in 1996, more and more people are living longer, healthier lives with HIV infection. A changing epidemiologic pattern of disease has been described in which incident HIV has a relatively stable rate of 19/100,000 people which yields an annual U.S. incidence of approximately 50,000 new infections/year. However, significant disparities have emerged with African-Americans experiencing incidence rates of 70/100,000 and those with Hispanic/Latino ethnicity demonstrating an incidence of 26/100,000 people. In comparison, Caucasians and Asians have an estimated incidence of 8-9 new infections per 100,000 people. Women have experienced a dramatic increase in risk of HIV infection and now represent 25% of all people living with HIV in the U.S. 78% of these women are African-American or identify their ethnicity as Hispanic/Latino. Among men, the key risk factor is male to male sexual contact (75%), but among women, 74% of infections are attributed to heterosexual contact. White men who have sex with men (MSM) continued to account for the largest number of new HIV infections in 2010 by transmission category. However white men have little age predilection to new HIV infection, whereas the highest risk for African-American and Hispanic/Latino men occurs in the 13-29 year old age range. An epidemiologic model suggests that half of all MSM will contract HIV by age 50, and if current trends continue half of today's young black MSM will have HIV by age 35.(2) The CDC reports that 50% of all persons with HIV are located in 12 U.S. cities (San Francisco, Los Angeles, Chicago, Dallas, Houston, Miami, Tampa, Atlanta, Washington DC, Baltimore, Philadelphia and New York). Minority groups including African-Americans and Hispanic/Latino young men are over-represented relative to their proportion in the U.S. population. Approximately 20% of HIV infected individuals are unaware of infection and account for half of all new infections in others. Though effective treatment for HIV is available and highly efficacious, linkage to appropriate care remains a significant barrier.(3) Figure 1 clearly illustrates the magnitude of this public health problem in the U.S.

In the HIV-infected patient, there is a complex and multifactorial interaction between common etiologies of liver disease. These include viral hepatitis, drug-associated hepatotoxicity, drug associated and unassociated non-alcoholic steatohepatitis (NASH), alcohol, and liver involvement with systemic infections and malignancies. In addition, HIV-infected patients have the same risk as the general population of having the spectrum of liver diseases seen in the general population including genetic hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease, etc. Estimates of the worldwide burden of viral hepatitis in those with HIV are illustrated in Figure 2. In addition, hepatitis D is quite

prevalent among HBV/HIV coinfecting patients in Europe, though it is diagnosed with far less frequency in the U.S. The overall prevalence of delta hepatitis among HBsAg positive patients in Europe is 14.5% with peak prevalence seen in Russia (25%) and Spain/Italy (21%).(4) A EUROSIDA multivariable model suggests that presence of hepatitis D is the most important factor in progression to liver-related death. The role of long term exposure to nucleoside analogues with dual viral activity on natural history remains unknown. Recognition of hepatitis E as a cause of both acute hepatitis and as an agent associated with development of chronic liver disease in immunosuppressed individuals is increasing. There are many critical research questions regarding incidence, prevalence and risk of chronicity in HIV-infected patients.(5-7)

The role of drugs in liver injury in those with HIV remains a persistent issue. Overall, acute toxicity associated with antiretroviral agents has decreased with the development and increased use of newer, less toxic medications. Liver injury may be idiosyncratic and may present as either an acute hepatotoxicity process or with chronic hepatotoxicity. In the chronic state, medications may represent an important factor in metabolic syndrome with non-alcoholic fatty liver (NAFL) or non-alcoholic steatohepatitis (NASH). Liver injury as evidenced by transaminase abnormalities is highly variable and has been reported in all classes. Some antiretrovirals such as the protease inhibitors, tipranavir or high dose ritonavir are strongly associated with hepatotoxicity. In all classes the presence of concurrent coinfection with HCV increases risk of liver injury.(8) Furthermore, treatment and clearance of HCV may decrease attributions of drug-associated hepatotoxicity. Older drugs including the deoxy-nucleotides (didanosine, stavudine) were highly injurious, often leading to mitochondrial injury and oxidative stress. Many of these agents are still in use. Risk of mitochondrial injury can be categorized by agent: didanosine (ddI) >stavudine (d4T)>zidovudine (ZDV or AZT)>>>tenofovir (TFV or TDF), lamivudine (Lam or 3TC), emtricitabine (FTC), abacavir (ABC). Furthermore, there is some evidence that prolonged exposure to agents such as ddI (didanosine) may be associated with development of non-cirrhotic portal hypertension.(9) Vispo et al, have proposed a two-hit model that leads to increased risk among patients with a specific genetic predisposition.(10) Drug-related hypersensitivity injury to the liver represents another mechanism of injury with a unique pattern of histology. It is seen in 5-8% of all patients exposed to abacavir but in the setting of HLA-B*5701, has a prevalence of 45%. HLA testing and avoidance of abacavir in patients with HLA-B*5701 prevents development of this type of hepatotoxicity. Similarly, nevirapine mediated hypersensitivity reactions occur in 5-7% of exposed persons, but are very frequent in those with low BMI, high CD4 count and with HLA DRB1*0101. The NIH has created a U.S. network to study drug hepatotoxicity including toxicity associated with antiretroviral agents. In the NIH Drug Induced Liver Injury Network (DILIN) database, the majority of HIV patients enrolled are men. Their age is higher than non-HIV infected patients in the database. 57% had hepatocellular injury and 43% had mixed or cholestatic injuries reported. Acute hepatitis E infection can mimic drug-induced liver injury and must be considered in the differential diagnosis.(11)

Overview of HIV Management for the Hepatologist

HIV TREATMENT (Masur, Mishra)—Antiretroviral therapy is now recommended by several US agencies for all HIV-infected persons (<http://aidsinfo.nih.gov/guidelines>). (12) Antiretroviral therapy used to be indicated only for persons with lower CD4+ lymphocyte count (for example, <350/mm³). However, there is accumulating evidence of a survival benefit for taking antiretroviral therapy at essentially all CD4+ lymphocyte counts.(13) An even greater urgency for antiretroviral therapy is emphasized for persons with HBV or HCV coinfection given accumulating data that antiretroviral therapy might attenuate the progression of liver fibrosis. In one recent study, a cohort of 638 coinfecting adults receiving

care at the Johns Hopkins HIV clinic between July 1993 and August 2011, persons receiving effective antiretroviral therapy had 73% fewer clinical events than those not on antiretroviral therapy.(14) Special emphasis is also given to giving antiretroviral therapy to other special patient groups such as pregnant women and persons with HIV infected nephropathy. This 'special' emphasis might override factors that would weigh against using antiretroviral therapy such as poor anticipated adherence.

The type of antiretroviral therapy that is used in someone with liver disease depends to some extent on the cause. With HIV/HBV coinfecting persons there is an emphasis on using tenofovir disoproxil fumarate (TDF) (alone or part of an emtricitabine co-formulation) as part of a suppressive HIV regimen because of the activity against both viruses and high threshold for HBV resistance. If tenofovir cannot be given, for example because of renal insufficiency, entecavir can be used. Many experts recommend that the 1 mg/day be used in all HCV/HIV coinfecting patients. Entecavir has some HIV activity and thus should only be used with a fully suppressive HIV regimen.(15) This is true with regard to lamivudine and emtricitabine as well, which will select for HIV resistant variants if used as HBV monotherapy. With HCV, the choice of antiretroviral therapy is largely influenced by anticipated interactions with anti-HCV medications including ribavirin and the HCV protease inhibitors boceprevir and telaprevir (Table 1a and b). In particular, zidovudine and didanosine are avoided due to interactions with ribavirin.(16, 17) The interactions between boceprevir or telaprevir and antiretroviral agents are complex and continue to evolve as new data becomes available (see below, HCV/HIV coinfection treatment).

In persons with cirrhosis, the question arises of what are the most liver friendly antiretroviral therapy regimens. Fortunately, most antiretroviral agents that are particularly hepatotoxic are not among the currently 'recommended' agents. For example, tipranavir use is discouraged in patients with advanced liver disease because of a nearly 3-fold increase risk of liver injury.(18) In addition, the so called 'd drugs' containing deoxy-nucleotide analogs (didanosine, stavudine) also may increase risk of hepatic steatosis and hepatoportal sclerosis, but are no longer routinely recommended.(19, 20) Drugs like nevirapine that can cause hypersensitivity reactions are also best avoided in persons with cirrhosis. In persons with decompensated (Childs C) cirrhosis, there may be a preference for avoiding some protease inhibitors (e.g. darunavir) though others (e.g. atazanavir) may be safely administered.

Pathogenesis of Accelerated Fibrogenesis in HCV/HIV Coinfection (Chung, Thomas, Kottlilil)

Natural history studies have shown that HIV coinfection promotes accelerated HCV hepatic fibrosis progression, even with excellent HIV control under ART. Moreover, in those who have progressed to cirrhosis, higher rates of liver failure and death are observed compared with patients with HCV mono-infection.(21) The mechanisms underlying accelerated hepatic fibrosis are being increasingly understood. While immunopathogenesis as a result of virus specific infiltrating T cells is a key driver of liver injury, it is unlikely that the dysregulated T-cell response in HIV coinfection can alone suffice to explain the accelerated natural history. Rather, a series of perturbations brought about by HIV infection in the liver microenvironment appears to contribute to the observed phenotype.(22)

Remarkably, HIV alters the natural history of HCV-related liver disease through at least five important mechanisms independently of its effects on T cells: (1) HIV signals through CXCR4 and CCR5 co-receptors on hepatocytes to upregulate HCV replication in a TGF- β 1-dependent manner (23); (2) HIV augments HCV-related increases in TGF- β 1 from hepatocytes, thereby enhancing fibrogenesis (23); (3) HCV and HIV independently induce TGF- β 1 through the generation of reactive oxygen species, which in turn induces p38 MAPK, JNK, and ERK, and converge on NF- κ B (24, 25); (4) HCV and HIV independently

induce hepatocyte apoptosis, providing another means by which these infections contribute to hepatic fibrosis progression (26); and (5) HIV is associated with a gut CD4 depletion enteropathy, promoting microbial translocation and induction of fibrogenesis through engagement of TLR4 on hepatocytes and stellate cells.(27, 28) Collectively, these findings provide evidence that HIV itself, independent of its effects on cellular immunity and despite its lack of tropism for hepatocytes, accelerates HCV-related liver disease progression. Besides addressing the HCV side of the equation with direct acting antiviral agents, the central role of reactive oxygen species (ROS) and apoptosis in driving fibrogenesis provides novel, attractive antifibrotic targets. The advent of improved, humanized mouse models that support both HIV and HCV infections will enhance our understanding of the multiple mechanisms promoting liver disease progression in HIV-infected persons.

Screening for hepatocellular carcinoma (HCC) (Thio, McGovern, Peters, Goodman, Stock)

Persons with chronic viral hepatitis are at increased risk of HCC and that risk may be even higher in those who are HIV-coinfected.(29, 30) In serial nationwide surveys in France, the proportion of liver-related deaths attributed to HCC rose from 15% in 2000 to 25% in 2005 and the percent due to HCV rose from 10 to 25%.(31)

There is a complex association between HIV infection and cancer. HIV infection clearly promotes some cancers, typically those caused by another virus. For example, Kaposi's sarcoma is caused by human herpes virus 8 and almost exclusively occurs in HIV-infected persons in the US. Likewise, the risk of Epstein-Barr virus associated non-Hodgkin lymphoma and human papilloma virus-associated cervical cancer are markedly increased in HIV-infected persons.(32) In other instances, associations between HIV and cancers might be confounded by more exposure to tobacco in HIV-infected persons than the HIV-uninfected control group.(33) With HCC, it is not clear whether HIV infection itself promotes cancer or just accelerates liver fibrosis in persons with chronic viral hepatitis, and that greater liver fibrosis increases the risk of HCC. If the latter is true, then the recommendations for HCC surveillance for HIV infected persons would be indexed to liver disease stage and would be essentially the same as for HIV uninfected persons. Further research into this issue is clearly indicated.

For persons without HIV, HCC screening is considered cost effective when the risk of HCC exceeds 1.5% per year for HCV and 0.2% per year for HBV.(34) In general, HCC surveillance is recommended for HCV infected persons only when there is bridging fibrosis or cirrhosis. For persons with chronic hepatitis B, the recommendations are more complex and include age, gender, HBV DNA level, disease stage, tobacco use, family history and other factors. The risk of HCC increases with age and it is likely that this risk is distinct from disease stage. HIV-infected persons have liver disease at fibrosis stages comparable to persons 10 years older.(35) However, it is not known if HCC risk is also effectively advanced a decade. There are emerging data suggesting HCC surveillance can reduce HCC related mortality.(36) The method typically recommended is ultrasound testing every 6 months.(34) Some authorities also recommend using alfa-fetoprotein testing and getting baseline testing with magnetic resonance imaging or bi-/triphasic computer tomography. There is at least one report suggesting every 4 month testing was superior to every 6 month testing in a high HCC incidence setting. There is a paucity of data to apply these principles to HIV-infected persons. Some studies suggest HCC is more aggressive in HIV-infected persons and that would diminish the value of current surveillance methods.(29, 30) In addition, limited access to liver transplants would also reduce the benefits of detection of HCC for those for whom transplantation is the optimal treatment. On the other hand, the higher risk of HCC might make surveillance more cost effective. At least one authoritative guideline recommends HCC screening for HIV-infected persons, effectively as in persons without HIV.(37) (see Table 2).

End Stage Liver Disease and Liver Transplantation (Stock, Soriano)

End-stage liver disease (ESLD) manifest as the presence of ascites, hepatic encephalopathy, bleeding varices or coagulopathy continues to represent a significant outcome in patients with HIV-associated liver disease. Not surprisingly, hepatic decompensation is directly associated with the stage of liver disease.(14) In one prospective cohort, the death rate for HIV-infected patients with compensated cirrhosis was 5.8%/year. The Model of End-stage Liver Disease (MELD) accurately predicted mortality in this cohort, and this has been validated in other cohorts as well.(38, 39) Liver transplantation in the HIV-infected patient with ESLD has been studied in several cohorts in the U.S. and Europe. The U.S. Solid Organ Transplant in HIV Trial provided key information regarding patient and graft survival in liver and kidney transplant recipients. Among liver transplant recipients with HBV/HIV coinfection, both patient and graft survival were comparable to that observed in non-HIV controls.(40) However, poorer outcomes were observed for both patients and grafts in the HCV/HIV coinfecting subjects. Predictors of graft survival were analyzed in both univariate and multivariate analyses. Predictors of improved graft survival included a BMI at enrollment of <21, avoidance of dual (liver/kidney) transplant, an negative HCV antibody positive donor and younger donor age.(41) Removal of patients with those risk factors restores graft survival to that equivalent to matched controls. The rate of acute rejection was 2-fold higher among HCV/HIV liver transplant recipients vs. those with HCV alone. 50% of episodes of acute rejection occurred during the first 21 days of transplant, suggesting that these patients have a unique immunologic milieu into which organs are transplanted.

Treatment

HIV/HCV coinfection (Fontana, Dieterich, Wyles, Conway)—Historically, HIV/HCV coinfecting persons had lower sustained virologic response (SVR) rates than persons without HIV infection when treated with pegylated interferon and ribavirin.(42) However, there are clear survival benefits among HIV/HCV coinfecting persons who achieved SVR.(14, 43) Fortunately, differences in the likelihood of SVR between persons with and without HIV coinfection are diminishing. In a phase 2 study of genotype1 HIV coinfecting persons, 28 (74%) of 38 persons randomized to telaprevir, peginterferon and ribavirin received a SVR12 compared to 10 (45%) of 22 patients randomized to placebo, peginterferon, and ribavirin. In that study, telaprevir/placebo was used for the initial 12 weeks, while peginterferon and ribavirin were given for 48 weeks.(44) Although the number of persons treated is small, the SVR rate in the telaprevir arm (72%) is similar to what was achieved in persons without HIV.(45, 46) Pharmacokinetic studies were embedded into the study and confirmed the safety of using telaprevir with tenofovir, emtricitabine, efavirenz (at higher telaprevir dose), or atazanavir. There were no unexpected adverse events including breakthrough of HIV.

Boceprevir was also studied in HIV/HCV coinfecting persons in phase 2. Following a 4-week lead in of peginterferon and ribavirin, genotype 1 HIV/HCV coinfecting persons were randomized to placebo or boceprevir for 48 weeks. SVR12 was achieved in 37 (60.7%) of 61 persons taking boceprevir versus 9 (26.5%) of 34 persons randomized to placebo. These results were also similar to what was achieved in HIV-uninfected persons.(47) There were no unexpected adverse events including breakthroughs of HIV despite evidence of significant interactions in healthy volunteers that led to lower drug levels for some antiretroviral drugs such lopinavir, atazanavir, and darunavir. This information was available after the Phase 2 trial was initiated, and there were no apparent clinically significant drug interaction in the study despite some patients being on these medications. This may be explained by the addition of pegylated interferon which has intrinsic antiretroviral activity and the continued use of antiretroviral in other classes. This issue is under intense evaluation in an ACTG Phase 3 study of boceprevir based triple therapy noted below.

Phase 3 studies of boceprevir and telaprevir with peginterferon and ribavirin are ongoing and the medications are not yet FDA approved for use in HIV/HCV coinfecting persons. Nonetheless, current guidelines support the use of HCV protease inhibitors with peginterferon and ribavirin for genotype 1 HCV-infected persons who need therapy and for whom drug interactions can be managed (<http://aidsinfo.nih.gov/guidelines>). (12, 48)

There are also studies underway to evaluate the efficacy of other direct acting HCV agents for treatment of HIV/HCV coinfecting persons. In one study, simeprevir 150 mg once a day was given for 12 weeks with peginterferon and ribavirin, which was then extended for variable durations up to 48 weeks total. Patients who had never been treated before or who had relapsed after peginterferon and ribavirin and who were undetectable at 4 weeks of simeprevir, peginterferon and ribavirin were randomized to 24 or 48 total weeks of treatment (response guided). Patients with prior null or partial response or cirrhosis were given 48 weeks of treatment. In a preliminary report, SVR12 was reported in 77% in the naïve and relapse group. (49)

Another HCV protease inhibitor, faldaprevir, has been studied in HIV/HCV coinfecting patients. In one arm patients received faldaprevir 120 mg daily, peginterferon and ribavirin for 24 weeks followed by peginterferon and ribavirin for 24 additional weeks. In the other arm, faldaprevir 240 mg per day was given and there was randomization at week 12 to stop faldaprevir versus continuing to week 24. All patients were treated for 48 weeks total with the balance being with peginterferon and ribavirin. Early virologic responses were >80%. (50)

There is also an NS5A targeting agent, daclatasvir, that is being tested in HIV/HCV coinfecting patients. Studies of drug:drug interactions in healthy volunteers examined interactions with daclatasvir and the antiretroviral agents atazanavir, efavirenz and tenofovir. Daclatasvir did not affect levels of the antiretrovirals in a clinically significant manner. However, daclatasvir levels were altered when co-administered with boosted atazanavir or efavirenz. (51) This interaction led to the predicted need for dose adjustment of daclatasvir in clinical trials. These trials are now underway. All patients get daclatasvir, peginterferon and ribavirin for 24 weeks. There is a response guided randomization that can occur in one arm with those who are HCV RNA undetectable at weeks 4 and 12 randomized to a total of 24 or 48 weeks of treatment. The other arm receives the final 24 weeks with peginterferon and ribavirin.

The HCV nucleotide inhibitor sofosbuvir is also being evaluated in HIV/HCV coinfecting patients. (www.ClinicalTrials.gov) In a 30 subject pilot trial of sofosbuvir monotherapy given for 7 days HCV viral decline was similar to that observed in HCV mono-infected subjects. A viral decline of approximately 4 logs was observed. CD4 count and HIV viral load were not affected. The patients were on multiple antiretroviral regimens. (52)

Drug:drug Interactions (McCance-Katz, Fontana, Mishra)

Drug:drug interactions have emerged as an important topic in relation to the use and development of new direct acting agents. Effects of these agents on cytochrome P450 enzymes, transporters and other processes like glucuronidation impact choices of other medications that patients are commonly receiving. Broadly speaking, the protease inhibitors and NS5a inhibitors have been most associated with significant drug:drug interactions. These interactions can be classified among patients with HIV infection into reciprocal interactions with antiretroviral agents and other drug classes.

There are many important pharmacologic interactions between HCV protease inhibitors and antiretroviral therapy. In general, tenofovir, emtricitabine, etravirine, rilpivirine and

raltegravir appear to be safe to use with either boceprevir or telaprevir, though caution is always indicated in the absence of large datasets. In addition, telaprevir appears to also be safe to use with atazanavir/r and efavirenz. However, patients on efavirenz require higher doses of telaprevir due to decreases in telaprevir AUC and C_{min}.(44) Table 1 describes known interactions between telaprevir and boceprevir with commonly used antiretroviral agents.

Interactions with other medications are common. Virtually any medication that requires metabolism through the Cyp3A/4 pathway may be impacted by use of the currently approved protease inhibitors. This includes many statins, proton-pump inhibitors as well as sedatives such as midazolam, tuberculosis medications including rifampin and PDE5 inhibitors like sildenafil. Very complex interactions exist with immunosuppressive medications used in the post-transplant setting. Use of tacrolimus or cyclosporine requires significant reduction in the dose of the immunosuppressive agent to avoid toxicity attributable to elevated drug concentrations.

These and other drug interactions should always be checked when making a change since new information comes regularly (www.hep-druginteractions.org).

Psychiatric and Social Issues in Liver Disease Care (Conway, Treisman, McCance-Katz)

While we see significant advances in our understanding of the pathophysiology of liver disease in those with HIV infection and major strides in development of new medications to treat hepatitis C, significant issues related to poverty, health-care access, concomitant psychiatric disorders and substance abuse remain as barriers to improved health. Indeed, many of these issues are intrinsically related to each other.(53) In substance-abuse cohorts traditional medical models that depend upon diagnosis linkage to treatment with subsequent improvement in prognosis may not apply. Veterans with psychiatric disorders are less likely to be offered HCV treatment .(54) Among injection drug users with HCV, treatment uptake rates ranging from 1.1% to 4% have been reported.(55, 56) Reasons for this are clearly multifactorial but include bias by treaters against treatment of injection use users (57), lack of health care funding for disease management and treatment of the uninsured, and an overall lack of providers able to provide care. System models that seem effective include use of multidisciplinary academic/community-based partnerships that incorporate physicians with training in addiction and hepatology, as well as nurses, outreach workers, and research coordinators. Re-infection with HCV remains an issue for many patients with ongoing risk behaviors leading caregivers to withhold treatment. Rates of re-infection with HCV reported in the literature vary, but rates as high as 5.27 cases/100 person years have been reported in incarcerated subjects(58) and 5.4 cases/100 person years in active IDU in the community. (59) There is some evidence that engagement in liver care and treatment reduces risk behaviors and there may be an immunologic component of protection against re-infection as well.(60)

Management of individual patients with substance abuse remains a significant barrier to HCV treatment, despite evidence that such treatment improves SVR rates among injection drug users treated for HCV infection and improves likelihood of receiving HIV care as well. (61) Psychiatric diagnoses are common among those with HIV and liver-related coinfections. At Johns Hopkins, 54% of patients presenting for medical evaluation had an Axis I psychiatric diagnosis, including major depression (20%), adjustment disorder (18%), cognitive impairment (18%) and substance abuse (74%). The presence of untreated mental disorders has a significant effect on the probability of overall survival.(62)

Research issues- opportunities & barriers (Brobst & Sherman)

There has been significant growth in research efforts associated with liver disease and HIV. One has to look no further than the increasing prominence given to liver-related topics at international meetings such as CROI (Conference on Retroviruses and Opportunistic Infections), which has significantly increased the proportion of time and space devoted to this subject between 2008 and 2013. The support provided by the NIH to HIV & Liver Disease 2012 by three institutes (NIAID, NIAAA, NIDA) also speaks to the importance given to this subject area by key funders of research. The strategic plans from several NIH institutes now include specific mention of liver disease as a research topic of interest. Moving forward there is a growing interest in the association of HIV with aging, including adaptations in liver physiology that occur in older HIV-infected individuals. The use of data and samples from large cohorts and repositories remain a key focus of NIH including the ACTG, WIHS, MACS, ALIVE, and others. The key barrier to research in this field is the global limitations of the funding environment within the NIH. Collaborations with industry partners remain an important source of both funds and for access to new medications that might otherwise not be tested in those with HIV infection.

Many key research questions remain unanswered. Though treatment of HCV in the HIV-infected patients now appears feasible, Phase 3 studies still lag behind developments in the monoinfected populations. Testing of easier, shorter therapies is critical, and rapid performance and dissemination of drug:drug interaction data must occur on a more rapid timeline. The importance of understanding drug:drug interactions has taken on new prominence with the recent observations that studies in healthy controls may not always mirror treatment outcomes in HIV-infected patients. Improved understanding of how HIV treatment impacts liver disease through modulation of immune activation and immune reconstitution and immunoregulation remains highly topical. The emergence of acute HCV in IDU and among MSM requires careful evaluation in terms of development of new public health prevention measures, as well as the update of paradigms for treatment intervention and prevention of re-infection. Management strategies for hepatitis B seem clear, but the importance of both occult HBV and hepatitis D remain less certain. Emerging data points to issues of long-term toxicity with historical antiretroviral agents (didanosine), and perhaps issues associated with long-term use of other classes that may contribute to oxidative stress. Health resource utilization research will be critical in the next few years. It is not enough to have new medications for HCV. We have to be able to identify those with coinfections, incorporate them into a healthcare system that can recognize and manage liver disease, and effectively treat curable etiologies of liver injury. For those with advanced liver fibrosis, recognition and management of portal hypertension and its complications as well as hepatocellular carcinoma surveillance are important, but unfulfilled requirements for this population. Liver transplantation for those with HIV is feasible, but outcomes are not optimal and research that permits better patient selection and pre- and post-transplant management is needed. Access to centers that can and will transplant those with HIV is essential and organ availability remains an issue for all patients with ESLD.

Acknowledgments

Funding for this conference was made possible [in part] by the National Institutes of Health under Award Number R13AI071925 from the National Institute of Allergy and Infectious Diseases (NIAID), with co-funding from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. 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 U.S. Government.

Supported by educational grants from: Merck, Genentech, Bristol-Myers Squibb, Gilead Sciences, Inc., Janssen Pharmaceuticals, Inc. administered by Janssen Services, LLC, and Kadmon Pharmaceuticals, LLC.

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Figure 1.

In 2008, the prevalence rate for persons aged 18–64 years living in the U.S. with an HIV diagnosis ranged by state from 40.1 to 3,365.2 per 100,000 persons * National HIV Surveillance System, United States, year-end 2008. * Rates are per 100,000 persons, categorized into quintiles and not adjusted for reporting delays. Overall rate: 417.5 per 100,000 persons. (MMWR 60:1618-1623).

Figure 2.
Estimated number of persons infected with hepatitis viruses worldwide (in millions)

Table 1

Drug interactions and 2012 recommendations for the use of boceprevir or telaprevir in HIV patients coinfecting with HCV based on current ART use

(a) Boceprevir					
ART	Effects on ART		Effects on Boceprevir		Recommendations
	AUC	C_{min}	AUC	C_{min}	
Efavirenz	↑ 20%	-	↓ 19%	↓ 44%	Do Not Co-Administer
ETR, NVP, RPV	No PK Data, Interaction Possible				Do Not Co-Administer
Atazanavir/r	↓ 35%	↓ 49%	No change		Do Not Co-Administer
Darunavir/r	↓ 44%	↓ 59%	↓ 29%	↓ 35%	Do Not Co-Administer
Lopinavir/r	↓ 34%	↓ 43%	↓ 44%	↓ 35%	Do Not Co-Administer
FPV/r, TPV/r	No PK Data, Interaction Possible				Do Not Co-Administer
Maraviroc	No PK Data, Interaction Possible				Do Not Co-Administer
Raltegravir	No significant changes				Use standard doses
Etravirine	↓23% ↓29% ↑10% ↓12%				Caution. No recommendation
Rilpivirine	No significant interactions				Use standard doses

(b) Telaprevir					
ART	Effects on ART		Effects on Telaprevir		Recommendations
	AUC	C_{min}	AUC	C_{min}	
Efavirenz	No change		↓ 26%	↓ 47%	↑ Telaprevir to 1.125mg q8h
Atazanavir/r	-	↑ 85%	↓ 20%	↓ 15%	Use standard doses
Darunavir/r	↓ 40%	↓ 42%	↓ 35%	↓ 32%	Do Not Co-Administer
Lopinavir/r	↓ 34%	↓ 43%	↓ 54%	↓ 52%	Do Not Co-Administer
FPV/r	↓ 47%	↓ 56%	↓ 32%	↓ 30%	Do Not Co-Administer
Maraviroc	No PK Data, Interaction Possible				Do Not Co-Administer
Raltegravir	↑ 31%	-	No significant changes		Use standard doses
Etravirine	No change	No change	↓ 16% ↓ 25%		Use standard doses
Rilpivirine	↑ 1.78x	↑ 1.93x	↓ 5% ↓ 11%		Use standard doses

Table 2

Guidelines for HCC screening/surveillance in those with HIV

	Screening	Method	Interval	Comments
CDC	Might be recommended for HBV Recommended for HCV with Cirrhosis	Ultrasound and alfa-fetoprotein	Optimal interval not known	<i>BIII</i> recommendation for HCV cirrhotics
AASLD	Same as HCV or HBV monoinfected	Ultrasound	6 months	<i>Level II evidence</i>
EASL-EORTC	Same as HCV or HBV monoinfected	Ultrasound	6 months (3-4 months when a nodule <1 cm is detected)	<i>I A/B</i>
APASL	Same as HCV or HBV monoinfected	Ultrasound and alfa-fetoprotein	6 months	“Coinfection with HBV and HCV may have synergistic effect on the development of HCC (2b)”