MEETING REPORT

Human Immunodeficiency Virus and Liver Disease Forum 2012

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In the United States, 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. 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 hepatitis C virus (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 recent 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. (HEPATOLOGY 2014;59:307-317)

Despite significant progress in our understanding of liver disease in patients infected with human immunodeficiency virus (HIV), progressive hepatic fibrosis, leading to portal hypertension (PH), and the development of hepatocellular carcinoma (HCC) 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 noncirrhotic PH.[1] Many HIV care providers have a limited understanding of the complexities associated with the management of liver disease. Similarly, many hepatologists are uncomfortable with addressing the nuanced relationship between the use of appropriate antiretroviral therapies (ARTs) and treatment of hepatitis B and C. To reduce this barrier to care, a multidisciplinary conference 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 (NIH; the National Institute of Allergy and Infectious Diseases [NIAID], the National Institute of Alcohol Abuse and Alcoholism [NIAAA], and the National Institute of Drug Abuse [NIDA]). Several pharmaceutical industry sponsors also provided unrestricted grants to the University of Cincinnati Continuing Medical Education Office (Cincinnati, OH), who provided oversight in accord with Accreditation Council for Continuing Medical Education guidelines to ensure rigorous, 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 previous HIV and liver disease conference was published in HEPATOLOGY. This article seeks to update the progress made in the interim 2-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, increasingly 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 in 100,000 people, which yields an annual U.S. incidence of approximately 50,000 new infections per year. However, significant disparities have emerged with African Americans experiencing incidence rates of 70 in 100,000 and those with Hispanic/Latino ethnicity demonstrating an incidence of 26 in 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 currently represent 25% of all people living with HIV in the United States. Seventy-eight percent 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 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 U.S. Centers for Disease Control and Prevention (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-American and Hispanic/Latino young men, are overrepresented 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 United States.

In the HIV-infected patient, there is a complex, multifactorial interaction between common etiologies of liver disease. These include viral hepatitis, drug-associated hepatotoxicity, drug-associated and -unassociated nonalcoholic 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 noted in the general population, including genetic hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease, and so on. Estimates of the worldwide burden of viral hepatitis in those with HIV are illustrated in Fig. 2. In addition, hepatitis D is quite prevalent among hepatitis B virus (HBV)/HIV-coinfected patients in Europe, though it is diagnosed with far less frequency in the United
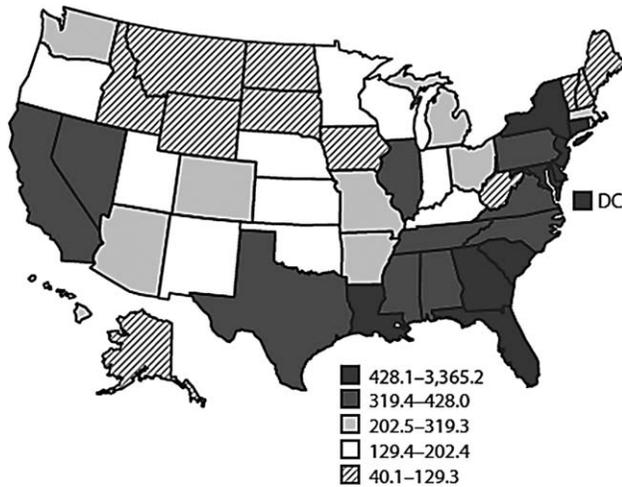
Fig. 1. In 2008, the prevalence rate for persons 18-64 years of age living in the United States with an HIV diagnosis ranged, by state, from 40.1 to 3,365.2 per 100,000 persons. *National HIV Surveillance System, United States, year-end 2008. *Rates are per 100,000 persons, categorized into quintiles and not adjusted for reporting delays. Overall rate: 417.5 per 100,000 persons (MMWR 60:1618-1623).

States. The overall prevalence of delta hepatitis among hepatitis B surface antigen-positive patients in Europe is 14.5%, with peak prevalence observed in Russia (25%) and Spain and Italy (21%).[4] A EUROSIDA multivariable model suggests that the presence of hepatitis D is the most important factor in progression to liver-related death. The role of long-term exposure to nucleoside analogs 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 the 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]
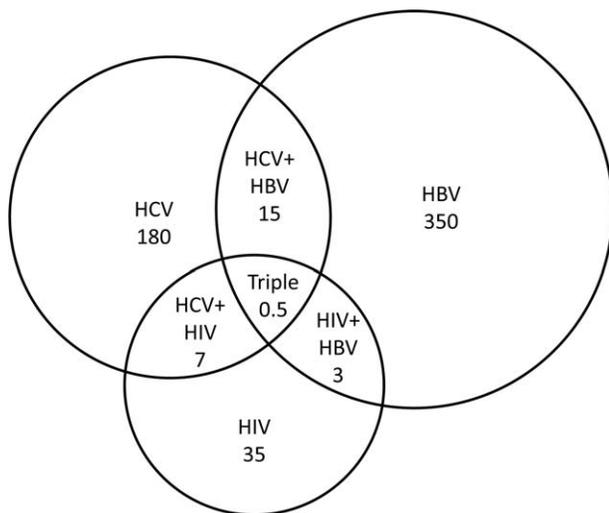
Fig. 2. Estimated number of persons infected with hepatitis viruses worldwide (in millions).

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 nonalcoholic fatty liver disease or 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 hepatitis C virus (HCV) increases the risk of liver injury.[8] Furthermore, treatment and clearance of HCV may decrease attributions of drug-associated hepatotoxicity. Older drugs, including the deoxynucleotides (e.g., didanosine and stavudine), were highly injurious, often leading to mitochondrial injury and oxidative stress (OS). Many of these agents are still in use. Risk of mitochondrial injury can be categorized by agent: didanosine (2′,3′-dideoxyinosine or ddI) > stavudine (d4T) > zidovudine (ZDV or AZT) ≫ tenofovir (TFV or tenofovir disoproxil fumarate [TDF]); lamivudine (Lam or 3TC); emtricitabine (FTC); and abacavir (ABC). Furthermore, there is some evidence that prolonged exposure to agents such as ddI (didanosine) may be associated with the development of noncirrhotic PH.[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 noted in 5%-8% of all patients exposed to abacavir, but, in the setting of human leukocyte antigen (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 body mass index (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 database, the majority of HIV patients enrolled are men. Their age is higher than non-HIV-infected patients in the database. Fifty-seven percent 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 currently recommended by several U.S. agencies for all HIV-infected persons (http://aidsinfo.nih.gov/guidelines).[12] ART used to be indicated only for persons with lower $CD4^+$ lymphocyte count (e.g., $<350/mm^3$). However, there is accumulating evidence of a survival benefit for taking ART 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 ART might attenuate the progression of liver fibrosis. In one recent study, a cohort of 638 coinfected 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 ART.[14] Special emphasis is also given to providing ART 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 ART that is used in someone with liver disease depends, to some extent, on the cause. With HIV/HBV-coinfected persons, there is an emphasis on using TDF (alone or part of an emtricitabine coformulation) 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 1 mg/day be used in all HCV/HIV-coinfected 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 ART is largely influenced by anticipated interactions with anti-HCV medications, including ribavirin (RBV) and the HCV protease inhibitors, boceprevir and telaprevir (Table 1A,B). In particular, zidovudine and ddl are avoided because of interactions with RBV.[16,17] Interactions between boceprevir or telaprevir and antiretroviral agents are complex and continue to evolve as new data become available (see below).

In persons with cirrhosis, the question arises of what are the most liver-friendly ART 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 deoxynucleotide analogs (didanosine and stavudine) also may increase risk of hepatic steatosis and hepatoportal sclerosis, but are no longer routinely recommended.[19,20] Drugs, such as nevirapine, that can cause hypersensitivity reactions are also best avoided in persons with cirrhosis. In persons with decompensated (Child-Pugh class 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, Kottilil). 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 monoinfection.[21] The mechanisms underlying accelerated hepatic fibrosis are being increasingly understood. Though 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 chemokine (C-X-C motif) receptor 4 and chemokine (C-C motif) receptor 5, coreceptors on hepatocytes to up-regulate HCV replication in a transforming growth factor beta 1 (TGF-β1)-dependent manner[23]; (2) HIV augments HCV-related increases in TGF-β1 from hepatocytes, thereby enhancing fibrogenesis[23]; (3) HCV and HIV independently induce TGF-β1 through the generation of reactive oxygen species (ROS), which, in turn, induces p38 mitogen-activated protein kinase, c-Jun N-terminal kinase, and extracellular signal-regulated kinase, and converge on nuclear factor kappa B[24,25]; (4) HCV and HIV independently induce hepatocyte apoptosis, providing another means by which these infections

Table 1. Drug Interactions and 2012 Recommendations for the Use of Boceprevir or Telaprevir in HIV Patients Coinfected With HCV Based on Current ART Use

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

	B. Telaprevir				
	Effects on ART		Effects on Telaprevir		
ART	AUC	C_{min}	AUC	C_{min}	Recommendations
Efavirenz	No change		↓ 26%	↓ 47%	↑ Telaprevir to 1.125 mg q8h
Atazanavir/r	–	↑ 85%	↓ 20%	↓ 15%	Use standard doses
Darunavir/r	↓ 40%	↓ 42%	↓ 35%	↓ 32%	Do not coadminister
Lopinavir/r	↓ 34%	↓ 43%	↓ 54%	↓ 52%	Do not coadminister
FPV/r	↓ 47%	↓ 56%	↓ 32%	↓ 30%	Do not coadminister
Maraviroc	No PK Data, Interaction Possible				Do not coadminister
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

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 Toll-like receptor 4 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 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 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 resulting from 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 United States. Likewise, the risk of Epstein-Barr virus associated non-Hodgkin's 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 whether HCC risk is also effectively advanced by a decade. There are emerging data suggesting that HCC surveillance can reduce HCC-related mortality.[36] The method typically recommended is ultrasound (US) testing every 6 months.[34] Some authorities also recommend using alpha-fetoprotein (AFP) testing and getting baseline testing with magnetic resonance imaging or bi- or triphasic computed tomography. There is at least one report suggesting that every-4-month testing was superior to every-6-month testing in a high-HCC-incidence setting. There are a paucity of data to apply these principles to HIV-infected persons. Some studies suggest that 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 (see Table 2).[37]

End-Stage Liver Disease and Liver Transplantation (Stock, Soriano). End-stage liver disease (ESLD) manifests 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% per year. The Model of End-stage Liver Disease accurately predicted mortality in this cohort, and this has been validated in other cohorts as well.[38,39] Liver transplantation (LT) in the HIV-infected patient with ESLD has been studied in several cohorts in the United States 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 LT 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-coinfected subjects. Predictors of graft survival were analyzed in both uni- and multivariate analyses. Predictors of improved graft survival included a BMI at enrollment of <21, avoidance of dual (liver/kidney) transplant, and 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 LT recipients versus those with HCV alone. Fifty percent 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-coinfected persons had lower sustained virologic response (SVR) rates than persons without HIV infection when treated with pegylated interferon (Peg-IFN) and RBV.[42] However, there are clear survival benefits among HIV/HCV-coinfected 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 II study of genotype1 HIV-coinfected persons, 28 (74%) of 38 persons randomized to telaprevir, Peg-IFN, and RBV received an SVR12, compared to 10

Table 2. Guidelines for HCC Screening/Surveillance in Those With HIV

Guidelines	Screening	Method	Interval	Comments
CDC	Might be recommended for HBV; recommended for HCV with cirrhosis	US and AFP	Optimal interval not known	BIII recommendation for HCV with cirrhosis
AASLD	Same as HCV or HBV monoinfected	US	6 months	Level II evidence
EASL-EORTC	Same as HCV or HBV monoinfected	US	6 months (3-4 months when a nodule <1 cm is detected	1 A/B
APASL	Same as HCV or HBV monoinfected	US and AFP	6 months	"Coinfection with HBV and HCV may have synergistic effect on the development of HCC (2b)."

Abbreviations: AASLD, American Association for the Study of Liver Diseases; EASL-EORTC, European Association for the Study of the Liver/European Organisation for Research and Treatment of Cancer; APASL, Asian-Pacific Association for the Study of Liver.

(45%) of 22 patients randomized to placebo, Peg-IFN, and RBV. In that study, telaprevir/placebo was used for the initial 12 weeks, whereas Peg-IFN and RBV 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] Pharmacokinetics (PK) 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-coinfected persons in phase II. After a 4-week lead-in of Peg-IFN and RBV, genotype 1 HIV/HCV-coinfected 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 II trial was initiated, and there were no apparent clinically significant drug interactions in the study, despite some patients being on these medications. This may be explained by the addition of Peg-IFN, which has intrinsic antiretroviral activity, and the continued use of antiretrovirals in other classes. This issue is under intense evaluation in an acquired immune deficiency syndrome (AIDS) Clinical Trial Group (ACTG) phase III study of boceprevir-based triple therapy noted below.

Phase III studies of boceprevir and telaprevir with Peg-IFN and RBV are ongoing, and the medications are not yet U.S. Food and Drug Administration approved for use in HIV/HCV-coinfected persons. Nonetheless, current guidelines support the use of HCV protease inhibitors with Peg-IFN and RBV 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-coinfected persons. In one study, simeprevir (150 mg once-daily) was given for 12 weeks with Peg-IFN and RBV, which was then extended for variable durations up to 48 weeks in total. Patients who had never been treated before or who had relapsed after Peg-IFN and RBV and who were undetectable at 4 weeks of simeprevir, Peg-IFN, and RBV were randomized to 24 or 48 total weeks of treatment (response guided). Patients with previous 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 groups.[49]

Another HCV protease inhibitor, faldaprevir, has been studied in HIV/HCV-coinfected patients. In one arm, patients received faldaprevir (120 mg daily), Peg-IFN, and RBV for 24 weeks, followed by Peg-IFN and RBV for 24 additional weeks. In the other arm, faldaprevir (240 mg/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 Peg-IFN and RBV. Early virologic responses were >80%.[50]

There is also a nonstructural protein 5A (NS5A)-targeting agent (daclatasvir) that is being tested in HIV/HCV-coinfected patients. Studies of drug-drug interactions (DDIs) 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 coadministered with boosted atazanavir or efavirenz.[51] This interaction led to the predicted need for dose adjustment of daclatasvir in clinical trials. These trials are currently underway. All patients get daclatasvir, Peg-IFN, and RBV 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 Peg-IFN and RBV.

The HCV nucleotide inhibitor, sofosbuvir, is also being evaluated in HIV/HCV-coinfected 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-monoinfected subjects. A viral decline of approximately 4 log was observed. CD4 count and HIV viral load were not affected. Patients were on multiple antiretroviral regimens.[52]

DDIs (McCance-Katz, Fontana, Mishra). DDIs 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 (CYP) enzymes, transporters, and other processes, such as glucuronidation, affect choices of other medications that patients are commonly receiving. Broadly speaking, the protease inhibitors

and NS5A inhibitors have been most associated with significant DDIs. 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 data sets. In addition, telaprevir appears to also be safe to use with atazanavir/r and efavirenz. However, patients on efavirenz require higher doses of telaprevir because of decreases in telaprevir area under the concentration-time curve (AUC) and minimum plasma concentration (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 affected 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 phosphodiesterase type 5 inhibitors such as sildenaphil. Very complex interactions exist with immunosuppressive medications used in the post-transplant setting. Use of tacrolimus or cyclosporine requires significant reduction in 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 because new information comes regularly (www.hep-druginteractions.org).

Psychiatric and Social Issues in Liver Disease Care (Conway, Treisman, McCance-Katz). Although we see significant advances in our understanding of the pathophysiology of liver disease in those with HIV infection and major strides in the 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 (IDUs) with HCV, treatment uptake rates ranging from 1.1% to 4% have been reported.[55,56] Reasons for this are clearly multifactoral, but include bias by providers against treatment of IDUs,[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 or community-based partnerships that incorporate physicians with training in addiction and hepatology, as well as nurses, outreach workers, and research coordinators. Reinfection with HCV remains an issue for many patients, with ongoing risk behaviors leading caregivers to withhold treatment. Rates of reinfection 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 IDUs 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 reinfection 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 IDUs treated for HCV infection and improves the 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 1 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 and 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 the 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 (the NIAID, the NIAAA, and the NIDA) also speaks to the importance given to this subject area by key funders of research. The strategic plans from several NIH institutes currently 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, Women's Interagency HIV Study, Multicenter AIDS Cohort Study, AIDS Link to the Intravenous Experience, 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 HIV-infected patients presently appears feasible, phase III studies still lag behind developments in monoinfected populations. Testing of easier, shorter therapies is critical, and rapid performance and dissemination of DDI data must occur on a more rapid timeline. The importance of understanding DDIs 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 affects liver disease through modulation of immune activation and immune reconstitution and immunoregulation remains highly topical. The emergence of acute HCV in IDUs and among MSM requires careful evaluation in terms of the development of new public health prevention measures, as well as the update of paradigms for treatment intervention and prevention of reinfection. 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 (ddI), and perhaps issues associated with long-term use of other classes that may contribute to OS. 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 health care 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 PH and its complications as well as HCC surveillance are important, but unfulfilled, requirements for this population. LT 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.

Appendix

Meeting participants (speakers whose lectures contributed to the content of this meeting summary) were as follows: Susan W. Brobst, Ph.D., National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD; John T. Brooks, M.D., Centers for Disease Control and Prevention, Atlanta, GA; Brian Conway, M.D., F.R.C.P.C., Vancouver ID Center, Vancouver, BC, Canada; Douglas Dieterich, M.D., Mount Sinai School of Medicine, New York, NY; Robert Fontana, M.D., University of Michigan, Ann Arbor, MI; Zachary Goodman, M.D., Ph.D., Inova Pathology Institute, Falls Church, VA; Shyam Kottilil, M.D., Ph.D., NIAID/NIH, Bethesda, MD; Henry Masur, M.D., NIH Clinical Center, Bethesda, MD; Elinore McCance-Katz, M.D., Ph.D., University of California San Francisco, San Francisco, CA; Barbara McGovern, M.D., Tufts University School of Medicine, Boston, MA; Poonam Mishra, M.D., Center for Drug Evaluation, U.S. FDA, Rockville, MD; Marion Peters, M.D., University of California San Francisco, San Francisco, CA; Vincent Soriano, M.D., Ph.D., Hospital Carlos III, Madrid, Spain; Peter G. Stock, M.D., Ph.D., University of California at San Francisco, San Francisco, CA; Chloe Thio, M.D., Johns Hopkins University, Baltimore, MD; Glenn J. Treisman, M.D., Ph.D., Johns Hopkins University School of Medicine, Baltimore, MD; and David Wyles, M.D., University of California San Diego, San Diego, CA.

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