Invited Review

CROI 2016: Viral Hepatitis and Liver Fibrosis

Anne F. Luetkemeyer, MD; David L. Wyles, MD

At the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, Massachusetts, hepatitis C virus (HCV) infection remained a major theme in the context of HIV-associated liver disease, although other causes of liver disease garnered increased attention, including fatty liver disease, hepatitis B, and the impact of HIV disease itself on the liver. Although no data from phase III studies of HCV direct-acting antiviral (DAA) drugs for the treatment of HIV/HCV coinfection were presented at CROI 2016, a broad range of HCV DAA–related topics were presented, including accumulating experience with real-world performance of DAA-based regimens outside of clinical trials, drug interactions between DAA and antiretroviral drugs, treatment of acute HCV infection, and retreatment of individuals whose DAA-based regimens failed and those in whom resistance to DAA drugs emerged. A summary of select abstracts from CROI 2016 is presented, including discussion of clinical relevance where appropriate and areas for future research.

The HCV Cascade of Care and Improving Access to HCV Treatment

The US Centers for Disease Control and Prevention recommends hepatitis C virus (HCV) screening for all individuals born between 1945 and 1965 (baby boomers).[1] Despite these recommendations, in data presented at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) from a Detroit cohort of more than 40,000 baby boomers seen in clinics from 2014 to 2015, only 21.3% were tested for HCV infection and 29% of those diagnosed with HCV infection received treatment (Abstract 531). Those with lower income or with Medicaid insurance were less likely to receive HCV treatment, highlighting the disparity in HCV treatment access for low-income individuals. Screening in the emergency department (ED) is one strategy to expand HCV screening to a broader population and did not prolong the length of stay in ED patients who received other lab testing in a California study of ED-based HCV testing (Abstract 532).

One of the challenges of scaling up treatment with direct-acting antiviral (DAA) drugs is the currently limited number of HCV practitioners. The Washington DC–based, observational ASCEND study demonstrated the feasibility of primary care–based HCV treatment with a fixed-dose combination of ledipasvir and sofosbuvir (Abstract 538LB). Three hundred four participants treated attained high rates of sustained virologic response 12 weeks after cessation of therapy (SVR12) across a variety of HCV practitioners; SVR12 rate was 96.7% with primary care physicians, 94.9% with nurse practitioners, and 92.1% with infectious diseases or hepatology specialists. In the subset of 62 participants coinfected with HIV, SVR rates remained high and did not differ substantially by practitioner type. It is important to note that participants were not randomly assigned to type of treating practitioner; however, fibrosis stage was evenly distributed across treatment groups. Notably, visit adherence was significantly higher among those treated by primary care physicians and nurse practitioners than among those treated by specialists (49%, 51%, and 19.2%, respectively; *P* = .002). This study provides support for community-based, nonspecialist HCV treatment, which can expand access to HCV therapy. A survey of Baltimore primary care physicians indicated that although very few primary care practitioners were prescribing HCV treatment and the majority did not think primary care practitioners should treat HCV infection, 65% wanted additional HCV training, and those with more than 20% of patients with HCV infection were much more likely to want to prescribe HCV treatment (Abstract 537). Thus, for selected primary care practitioners with a large population of HCV-infected patients, primary care–based HCV treatment may be a viable strategy to expand to the pool of HCV practitioners and the uptake of HCV therapy.

Observational and Real-World Experiences With HCV Infection

Overall, data from CROI 2016 demonstrate robust performance of DAA regimens in "real-world" populations that may differ markedly from populations enrolled in highly selected clinical trials. A US Department of Veterans Affairs database of HCV-monoinfected individuals examined a variety of sofosbuvir-based regimens and demonstrated overall SVR12 rates similar to those attained in clinical trials (Abstract 581). As expected, response rates were lower in those with cirrhosis but, reassuringly, were not negatively impacted by black race, diabetes, or higher baseline HCV RNA level. Similarly,

2 French databases each reported an overall SVR12 rate of 92% in HIV/HCV-coinfected and HCV-monoinfected individuals with a variety of HCV genotypes treated with all-oral DAA regimens (Abstracts 582 and 583).

The German Hepatitis C Cohort (GECCO), also consisting of HCV-monoinfected and HIV/HCV-coinfected participants with HCV genotypes 1 through 4 receiving all-oral DAA regimens, demonstrated an overall SVR12 rate of 92%, which was not impacted by the presence of cirrhosis, diabetes, or HIV coinfection. Among 283 HIV/HCV-coinfected individuals in GECCO, SVR rates were high (86%-98%) and did not differ substantially by antiretroviral regimens containing dolutegravir, raltegravir, HIV protease inhibitors (PIs), or HIV nonnucleoside analogue reverse transcriptase inhibitors (Abstract 589). Notably, 8 weeks of treatment with ledipasvir and sofosbuvir resulted in an SVR rate of 92% among those selected

> *Data on treatment with HCV DAA drugs outside of clinical trials demonstrate excellent responses; however, progress is needed with regard to HCV screening and linkage to care, as well as treatment outside of specialized centers.*

for shortened therapy, including 26 HIV/HCV-coinfected individuals, for whom data are lacking to date to support 8 weeks of treatment with ledipasvir and sofosbuvir (Abstract 584). Although this is a small number of individuals, these data are reassuring about the potential of 8 weeks of treatment for those with HIV/HCV coinfection, especially after the disappointing SVR12 rate of 76% with 8 weeks of another nonstructural protein 5A (NS5A) inhibitor–based regimen of sofosbuvir and daclatasvir in the previously published ALLY-2 study.[2]

In a New York City federally qualified health center (FQHC) cohort, 89 HCV-monoinfected and HIV/HCV-coinfected individuals treated with sofosbuvir-based regimens attained an overall SVR12 rate of 96%, which did not differ between those who used drugs and those who did not (96% and 95%, respectively; P = .95); drug use was defined as current opiate substitution therapy, a positive result on a urine toxicology screen, or a history of active drug use by chart review. This report adds to the growing data demonstrating that individuals with active or prior drug use can be effectively treated with DAA regimens (Abstract 585). A Texas clinic serving a similar low-income urban population demonstrated an impressive ramp up of DAA provision from less than 5 per month to an average of 20 or more per month over 1 year, despite limited resources, using a multidisciplinary approach. The overall SVR rate of 76% was limited by a 16% rate of loss to follow up, highlighting the need for support services for vulnerable populations even with well-tolerated all-oral therapy. Notably, those who completed treatment had an SVR12 rate of 90% (Abstract 587). Project INSPIRE (Innovate and Network to Stop HCV and Prevent Complications via Integrating Care, Responding to Needs and Engaging Patients and Providers) in New York City also used a multidisciplinary approach with

care coordination to successfully link more than 500 individuals to HCV care and to initiate HCV treatment for nearly 350 individuals in a population enriched for former and current injection drug use (IDU), mental illness, and other comorbidities (Abstract 534).

Drivers of the HCV Epidemic: Injection Drug Use and Sexual Transmission Among HIV-Infected Men Who Have Sex With Men

Globally, IDU is the major risk factor for HCV acquisition.[3] In the setting of the IDU-associated HIV and HCV outbreaks in Indiana, a detailed molecular epidemiologic analysis of the HCV transmission networks was presented (Abstract 149). The analysis was based on testing of 492 samples, including 311 samples of consensus NS5B sequences for genotyping and 281 samples of the hypervariable region 1 (HVR1) in the HCV envelope region (E1E2 envelope glycoprotein complex) analyzed using next-generation sequencing. The HCV genotypes based on NS5B sequences were 1a (72%), 3 (21%), 2 (5%), and 1b (2%), with 3 clusters including a large cluster of genotype 1a. More strikingly, based on HVR1 sequences, mixed or HCV superinfections were found in 20% of samples tested, indicating ongoing exposures and numerous reintroductions of HCV strains into the population.

Several abstracts highlighted the importance of sexual transmission of HCV infection among HIV-infected men who have sex with men (MSM) as an important and often underrecognized driver of the HCV epidemic. In the US-based HIV Outpatient Study (HOPS) from 2011 to 2013, HCV incidence declined among people who inject drugs (PWID) and heterosexual HIV-infected patients. However, the HCV incidence rate remained stable at approximately 1.1% per year among HIV-infected MSM, an important reminder that this population needs ongoing HCV screening as well as counseling about HCV prevention (Abstract 544).

Recent HCV infection (≤2 years) in an Australian cohort of HIV-infected MSM was statistically significantly associated with sexual exposure compared with IDU (adjusted odds ratio [aOR], 9.91; 95% confidence interval [CI], 3.84, 25.59) and a higher number of male sexual partners. Distressingly, almost half (43%) reported they "never" disclosed their HCV serostatus to sexual partners, and 27% were unaware of the potential for HCV reinfection after curative therapy (Abstract 545).

Prevalent HCV infections in a Vancouver, Canada, cohort of HIV-infected and HIV-uninfected MSM were statistically significantly associated with engaging in anal sex without condoms and crystal methamphetamine use (via injection

> *Sexually transmitted HCV infection remains an underrecognized issue among HIV-infected MSM.*

or other routes). The 5 incident HCV infections detected occurred only in HIV-infected MSM, and 4 of these were attributed to sexual contact rather than IDU (Abstract 546). Of

interest, a genetic variation in the low-density lipoprotein receptor gene may be associated with genetic susceptibility to sexual (but not parenteral) acquisition of HCV infection, a potential biologic explanation for why some men who have been exposed repeatedly to HCV via sexual contact with MSM remain uninfected (Abstract 547).

HCV Tratment as Prevention and HCV Vaccine Prospects

Treatment of those at highest risk of transmitting HCV, including PWID and HIV-infected MSM, will be key to realizing the potential of DAA-based treatment to curb and ultimately eliminate the HCV epidemic. Modeling data indicate that treating a minimum of 200 to 300 PWID could lead to elimination of the HCV epidemic in British Columbia, Canada; however, treatment must be paired with reinfection efforts to realize this potential (Abstract 533). In a similar vein, data from a Dutch modeling study suggest that treating all HCV/HIV-coinfected MSM will reduce HCV prevalence, but treatment must be linked with reduction in reinfection to lead to HCV elimination (Abstract 536).

Identifying broadly neutralizing antibodies and the epitopes they target may be one approach to identifying better HCV vaccine candidates. Utilizing an ongoing cohort of PWID, researchers from Amsterdam, the Netherlands, isolated and immortalized HCV E1E2–specific B cells from PWID who had repeatedly cleared HCV infection after numerous exposures (Abstract 152). Antibodies from these B-cell cultures were then purified and their epitopes characterized by alanine-scanning mutagenesis. Antibodies isolated from participants who cleared all HCV infections recognized multiple HCV genotypes. Broadly neutralizing antibodies tended to target epitope II plus domain B on envelope glycoprotein E2 (the so-called AR3 epitope) or the AR4 epitope at the interface of envelope glycoproteins E2 and E1. When tested using an HCV pseudoparticle assay, only antibodies to the AR3 epitope displayed broad neutralizing characteristics.

Acute HCV Infection

Acute HCV infection is an important opportunity to identify and treat new HCV infections, preventing subsequent liver damage and breaking the cycle of ongoing transmission. A Spanish observational study highlighted the disproportionate impact acute HCV infection can have on HIV-infected individuals, among whom a diagnosis of acute HCV infection led to a statistically significantly higher risk of hospitalization or death than among those with acute HCV infection who did not have HIV infection (adjusted hazard ratio [aHR], 2.91, for death; 95% CI, 2.38-3.53) (Abstract 590).

In the interferon alfa era, treatment during the first 6 months to 12 months of acute HCV infection was associated with higher cure rates with shorter duration of therapy. However, the efficacy of shortened interferon alfa–free, DAA-based therapy for acute HCV infection remains unknown. Previously reported at the 66th Annual Meeting of the

American Association for the Study of Liver Diseases, the first phase of the SWIFT-C (Sofosbuvir-Containing Regimens Without Interferon for Treatment of Acute HCV Infection) study demonstrated a disappointing 41% relapse rate after 8 weeks of treatment with sofosbuvir and weight-based ribavirin given to 17 HIV/HCV-coinfected participants with acute HCV genotype 1 infection.[4] In a pharmacokinetic evaluation of these individuals, median ribavirin level at end of treatment for those who relapsed was 34% lower than for those who attained an SVR12 ($P = .01$), suggesting that inadequate levels

> *The optimal treatment approach for acute HCV infection in those with HIV infection using DAA drugs remains to be defined.*

of ribavirin may have contributed to the failure of this strategy (Abstract 99). However, for HCV genotype 1 infections, sofosbuvir and ribavirin is no longer recommended for initial treatment, given the superior performance of NS5A-based regimens.[5]

With regard to the efficacy of NS5A-based treatment for acute HCV infection, 6 weeks of treatment with ledipasvir and sofosbuvir led to an SVR12 rate of 77% among 26 HIV-infected individuals with acute HCV infection (documented infection for < 24 weeks) and HCV genotype 1 or 4 (Abstract 154LB). Four virologic failures (1 of which was a reinfection) occurred in participants with the highest levels of HCV RNA at baseline (> 7.0 $\log_{10}$ IU/mL). This suggests that individuals with acute HCV infection and high baseline viral loads (in this study, ≥9 million IU/mL) may not be candidates for shorter therapy; however, shorter regimens may be feasible for those with lower baseline viral loads. Two of the 3 individuals who experienced virologic relapse each had 1 baseline NS5A resistance-associated variant (RAV) (1 at position 28 and 1 at position 31). It is unclear how these RAVs contributed to the treatment failures, and data were not presented on baseline RAVs from those who attained an SVR12. Even excluding reinfections and loss to follow-up, the 88% SVR12 rate is suboptimal in an era in which SVR12 rates for chronic HCV infection treated for 12 weeks are greater than 95%.[6] Data from an ongoing study of 8 weeks of sofosbuvir and ledipasvir for treatment of acute HCV infection are eagerly awaited.

Interactions Between HIV Antiretroviral and HCV DAA Drugs

Drug interactions between antiretroviral and DAA drugs are a major consideration in HCV treatment and may impact HCV regimen selection for HIV/HCV-coinfected patients.[5] When coadministered with tenofovir disoproxil fumarate (TDF), ledipasvir increases tenofovir levels, as do antiretroviral regimens boosted by ritonavir or cobicistat. Thus, the higher tenofovir concentrations observed with coadministration of ledipasvir and sofosbuvir with TDF-containing, boosted antiretroviral regimens may potentially increase the risk of nephrotoxic effects.

In a Spanish cohort of 225 HIV-infected individuals treated with ledipasvir and sofosbuvir, coadministration of TDF with ritonavir or cobicistat was not associated with statistically significant changes in renal function, with either 12 weeks or 24 weeks of HCV treatment. Five participants had an estimated glomerular filtration rate (eGFR) below 70 mL/min (by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) during HCV treatment, but none declined below 50 mL/min. Of those with an eGFR below 70 mL/min, 3 were taking boosted antiretroviral regimens, and eGFR returned to above 70 mL/min in all 5 at the cessation of HCV treatment. One participant taking a regimen of cobicistat-boosted elvitegravir, emtricitabine, and TDF discontinued the regimen because of a decline in eGFR from 89 mL/min to 56 mL/min; eGFR after HCV treatment was 85 mL/min (Abstract 452). In a German study of treatment for acute HCV infection, 7 of 26 participants were taking ritonavir- or cobicistat-containing regimens with TDF while receiving HCV treatment with ledipasvir and sofosbuvir; no renal adverse events were reported (Abstract 154LB).

Currently, the regimen of paritaprevir, ritonavir, and ombitasvir plus dasabuvir (PrOD) can be coadministered with HIV regimens containing unboosted integrase strand transfer inhibitors or boosted atazanavir. Data from uninfected volunteers demonstrated a decrease in darunavir trough concentration of approximately 45% when coadministered with PrOD,[7] resulting in the recommendation that this regimen not be coadministered with these HIV medications pending further data. HCV and HIV outcomes as well as pharmacokinetic data from an ongoing phase II/III study of PrOD among HIV/HCV-coinfected individuals, including those taking ritonavir-boosted darunavir, were presented (Abstract 574). Twenty-two participants with suppressed HIV RNA who were taking an antiretroviral regimen of ritonavir-boosted darunavir once daily were randomly assigned to continue the daily regimen or to increase to 600 mg/100 mg twice daily 2 weeks before initiating HCV treatment with PrOD plus ribavirin for 12 weeks. The majority of participants was HCV treatment naive (19/22) and only 3 had cirrhosis. All participants achieved an SVR12. Five participants experienced HIV RNA blips (< 200 copies/mL) during treatment, with no difference between the daily (n = 2) or twice-daily (n = 3) arms. Compared with pretreatment levels, darunavir trough concentrations decreased by 36% and 17%, respectively, in those taking daily and twice-daily treatment. These data suggest that ritonavir-boosted darunavir may be coadministered with PrOD. More data will be available on completion of the phase III portions of the study; however, the population for which data are most needed, those taking darunavir twice daily who have a history of HIV PI–resistance associated mutations, was not addressed in this study.

Two abstracts described drug interactions of 2 investigational HCV regimens: 1) sofosbuvir and the investigational pangenotypic NS5A inhibitor velpatasvir (Abstract 100), and 2) the investigational NS3 PI ABT-493 and the investigational NS5A inhibitor ABT-530 (Abstract 453). In a study of uninfected volunteers, the impact of ritonavir- or cobicistat-boosted regimens when given with sofosbuvir and velpatasvir was evaluated (Abstract 100). Modest increases in the area under the curve (AUC) of sofosbuvir ($< 50\%$) were observed when coadministered with cobicistat or with ritonavir-boosted atazanavir; large increases in the AUC (2.0-2.5 fold) and maximum plasma concentration C_{max} (4 fold) of velpatasvir were observed when coadministered with ritonavir-boosted atazanavir. Conversely, a roughly 50% increase in the AUC, C_{max}, and minimum plasma concentration C_{min} of tenofovir was observed when given as TDF in combination with cobicistat or ritonavir. The investigators concluded that the data support coadministration of any of these antiretroviral regimens with sofosbuvir and velpatasvir. Pending data from phase III studies, the increase in levels of tenofovir exposure observed when given as TDF in combination with sofosbuvir and velpatasvir is similar to that seen with sofosbuvir and ledipasvir, suggesting that enhanced monitoring for tenofovir toxic effects during coadministration is warranted.

Interactions between the investigational regimen of ABT-493 and ABT-530 and rilpivirine or raltegravir were evaluated in uninfected volunteers (Abstract 453). As expected, given the neutral impact of rilpivirine or raltegravir on coadministered drugs, no substantial changes in levels of ABT-493 or ABT-530 exposure were observed ($< 15\%$ change). An approximately 2-fold increase in rilpivirine exposure was observed, although trough levels of raltegravir increased approximately 2.5 fold with a large degree of variability. Overall, the changes identified were similar in magnitude to drugs currently safely coadministered with rilpivirine or raltegravir, suggesting that ABT-493 and ABT-530 can also be coadministered with these drugs.

Resistance-Associated Variants and HCV Retreatment

Clinical data show that the impact of NS5A RAVs is quite different for HCV genotype 1a than for HCV genotype 1b.[8] In a series of in vitro experiments, Newton and colleagues (Abstract 578) explored polymorphic site 28 in NS5A and its impact on other NS5A RAVs. Using a replicon system with genotype 1a or 1b NS5A sequences, the consensus amino acid at position 28 (methionine [M] in 1a; leucine [L] in 1b) was swapped (M28L in 1a, and L28M in 1b) and its impact on fold changes in susceptibility to the NS5A inhibitors daclatasvir, ledipasvir, and ombitasvir in conjunction with other RAVs at positions Q30, L31, and Y93 were assessed. Changing the consensus amino acid at position 28 had little impact by itself on either NS5A background, although the M28L in genotype 1a did result in consistent decreases in inhibitor half maximal effective concentrations (ie, hypersusceptibility). Changes in M or L at position 28 did not have a measurable effect on replication capacity in either background. The M28L variant in genotype 1a substantially lessened the impact (a $10 \times$ to $> 1000 \times$ decrease in half maximal inhibitory concentration) of NS5A RAVs Q30E/H/K/R, L31M, and Y93H, essentially making the genotype 1a replicon behave more like genotype 1b with respect to the impact of these RAVs

on daclatasvir, ledipasvir, and ombitasvir. The converse was also true: introducing the L28M variant in genotype 1b substantially increased resistance to daclatasvir, ledipasvir, and ombitasvir for RAVs L31M and Y93H.

In a survey of NS5A RAVs from 973 HCV samples submitted for testing, including 776 with genotype 1a and 197 with genotype 1b, resistant variants were identified in 39.6% of 1a and 43.1% of 1b isolates (Abstract 579). RAVs at positions 28, 30, 31, 58, and 93 were counted when present in more than 10% of the viral population on deep sequencing using the Illumina MiSeq platform. Unfortunately, clinical data were not available for the samples (eg, whether the individuals were DAA treatment experienced or naive). Given the nature of the RAVs identified and the percentages with multiple RAVs (40% of genotype 1a, and 26% of genotype 1b), it is likely a substantial proportion were DAA treatment failures exposed to an NS5A inhibitor. The most prevalent RAVs in genotype 1a were at position Q30 and Y93, and in genotype 1b the specific Y93H RAV was most prevalent. Susceptibilities of the various RAVs to daclatasvir, ledipasvir, and ombitasvir (in replicons or using participant-derived NS5A sequences) in genotypes 1a and 1b backgrounds were tested and, in line with previous results, showed larger shifts in activity ("more" resistance) in genotype 1a than in 1b replicons, particularly at position 93. Multiple RAVs present in genotype 1a also tended to cause higher-level resistance than any single RAV.

Baseline NS5A RAVs impact responses to NS5A-containing DAA regimens, particularly in populations with other predictors of a poorer treatment response, such as prior treatment failure and cirrhosis. Several studies evaluated the impact of baseline RAVs on treatment outcomes in clinical trial and real-world settings. Fourati and colleagues conducted a survey of baseline N5SA and NS5B RAVs in 177 individuals and their impact on treatment outcomes with 12 weeks of sofosbuvir and daclatasvir (Abstract 577). The presence of RAVs at key NS5A (ie, 28, 29, 30, 31, 32, 58, 62, 92, and 93) and NS5B (ie, 159, 282, 316, 320, and 321) positions was assessed using population sequencing. Individuals were infected with HCV genotype 1a (n = 44), 1b (63), 3 (29), or 4 (41) and were treatment naive or had previously taken peginterferon alfa and ribavirin, with or without an HCV PI. Cirrhosis was present in 44%, including 55% of those with HCV genotype 3 infection. Baseline NS5A RAVs were identified in 9% of those with genotype 1a (M28V/T and Q30R) and 21% of those with genotype 3 (A30K/S, A62L, and Y93H). No S282T NS5B RAVs were detected at baseline. Only 8 of the 177 individuals experienced virologic failure, and having genotype 3 (5/8) or cirrhosis (7/8) were the most common characteristics associated with treatment failure. There was a trend toward an association between having the Y93H variant at baseline and virologic failure (96% and 75% SVR12 rates for those without and with Y93H, respectively; P = .06). Importantly, the regimen used, sofosbuvir and daclatasvir without ribavirin, is not recommended for individuals with HCV genotype 3 infection who have cirrhosis.[5]

In terms of predictors of DAA treatment failure, 13 individuals who experienced virologic failure after treatment with

ledipasvir and sofosbuvir in a cohort at Mount Sinai Medical Center in New York, New York, were evaluated; 8 (62%) had cirrhosis, 5 (38%) had a history of hepatocellular carcinoma (HCC), and 6 (46%) had a prior treatment failure with an interferon alfa–based regimen (Abstract 588). Black race (OR, 4.96; 95% CI, 1.18-13.09) and male sex (OR, 4.62; 95% CI, 1.28-16.6) were statistically significantly associated with treatment failure, as has been observed in other real-world cohorts that have reported treatment failures associated with black race and male sex.[9,10] Baseline NS5A resistance data were not available, but as expected, the majority of individuals (15/17) who underwent resistance testing after virologic failure had 1 or more NS5A RAVs.

In another study that assessed the impact of baseline RAVs on treatment response, NS3 and NS5A RAVs were assessed retrospectively in interferon alfa–experienced participants with HCV genotype 1a infection treated with PrOD and ribavirin in the SAPPHIRE-II and TURQUOISE-II studies, as well as those with genotype 1b infection treated with PrOD without

> *The impact of HCV RAVs on responses to DAA-based treatment cannot be assessed in a vacuum. Regimen and patient characteristics also have a substantial impact on treatment response in addition to consideration of RAVs.*

ribavirin in the PEARL-II and TURQUOISE-III studies (Abstract 539LB). Various RAV definitions (eg, drug class RAVs vs drug-specific RAVs) were assessed using next-generation sequencing and reported at various thresholds (1%-15%); ombitasvir-specific NS5A RAVs were present in 12% of participants with genotype 1a at the 15% threshold. In this analysis, baseline ombitasvir RAVs had no substantial impact on treatment of those with genotype 1a with PrOD plus RBV (95% and 97%, for those with and without RAVs, respectively). Baseline NS3 RAVs or RAVs in those with genotype 1b also did not impact treatment response. Unfortunately, the group of most clinical interest with the highest likelihood of being impacted by baseline RAVs, those with genotype 1a treated without ribavirin (in the PEARL-IV study), were omitted from this analysis.

The phase III ALLY-2 study evaluated treatment with sofosbuvir and daclatasvir for 12 weeks or 8 weeks in HIV/HCV-coinfected participants.[2] In a follow-up study, the presence of NS5A or NS5B RAVs at baseline and treatment failure were assessed using next-generation sequencing to determine if RAVs missed by population sequencing appeared to impact clinical responses (Abstract 575). For 14 participants who experienced virologic failure (3 with 12 weeks and 11 with 8 weeks of treatment with sofosbuvir and daclatasvir), samples taken at baseline and at treatment failure were analyzed using the Illumina MiSeq platform. A 1% detection threshold was used to identify RAVs in NS5A and NS5B. In participants for whom 12 weeks of therapy failed, next-generation sequencing did not detect additional NS5A

RAVs compared with population sequencing. In 3 of 11 participants for whom 8 weeks of therapy failed, additional NS5A RAVs were detected with next-generation sequencing at time of failure; however, all were at low prevalence (< 2 %) by week 24 of follow-up. No minor variants of clinical significance (eg, S282T) were found with next-generation sequencing in NS5B. Overall, these data support the emerging theme that population sequencing identifies the vast majority of clinically significant NS5A RAVs.

After failure of a DAA regimen, treatment-emergent RAVs may be selected, and the impact of these RAVs on retreatment may be different than that of baseline RAVs. Two studies of RAVs and retreatment response were presented. Wilson and colleagues presented a detailed analysis of RAVs and SVR outcomes for individuals retreated with a fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks following failed short-course therapy (4-6 weeks) with this regimen plus 1 to 2 additional agents (Abstract 580). The investigators first examined whether baseline NS3 and NS5A RAVs impacted treatment response to the initial regimen. With 8 weeks of treatment consisting of sofosbuvir and ledipasvir plus the investigational NS3 PI GS-9451, baseline RAVs did not have a clear impact on treatment response, although there was limited power to detect a substantial impact based on the small numbers. Individuals with baseline NS5A RAVs did have a numerically lower response rate to 6 weeks of sofosbuvir and ledipasvir plus GS-9451 (60% [3/5] of those with NS5A RAVs vs 85% [17/20] of those without NS5A RAVs). SVR rates in those who received 4 weeks of treatment with sofosbuvir and ledipasvir plus GS-9451 or sofosbuvir and ledipasvir plus GS-9451 and GS-9669 (an investigational thumb site II nonnucleoside inhibitor of NS5B) were low overall (40% and 20%, respectively), despite a treatment-naive population with Metavir fibrosis stages F0 to F2. Thirty-four individuals (33 treatment failures at 4 weeks, and 1 at 6 weeks) were retreated with sofosbuvir and ledipasvir for 12 weeks. Before retreatment, 29 had NS5A resistance, including 28 with greater than 100 times ledipasvir resistance. The SVR rate was 90% (26/29) in those with NS5A RAVs and 100% (5/5) in those without NS5A RAVs.

The second study reported retreatment results for 9 participants whose treatment failed in the ION-4 study (sofosbuvir and ledipasvir for 12 weeks)[6] who were then re-treated with sofosbuvir and ledipasvir plus ribavirin for 24 weeks (Abstract 573). All 9 participants were black and had the IL28B non-CC genotype, 7 had HCV genotype 1a infection, and 7 were men. Only 2 participants had cirrhosis, and 7 were taking efavirenz. Participants were retreated quickly, with a mean time from treatment failure of 43 days; despite this, baseline HCV RNA level was 6.4 $\log_{10}$ IU/mL. Kinetics of viral suppression during treatment did not appear to be impacted by prior treatment failure; 100% of participants had an HCV RNA level below the lower limit of quantification at week 4, and this was maintained through the end of treatment. One participant experienced virologic failure, with relapse 4 weeks after cessation of treatment. The SVR12 rate was 89% (8/9). RAVs associated with high-fold reduced

susceptibility to ledipasvir (L31M + H58D, Y93N/H, or L31M/V) were present in more than 99% of the quasispecies in 7 of 9 participants but did not have a clear impact on retreatment response (6/7; 86% with an SVR). In the lone participant who relapsed, L31M was present at retreatment and retreatment failure.

A second abstract related to the ION-4 study presented data from a genome-wide association study undertaken to identify previously unrecognized host genomic determinants that may have contributed to treatment failure (Abstract 601). Ultimately, no notable genome-wide associations with treatment failure were found.

Collectively, these studies highlight that the impact of RAVs, at baseline or that emerged during treatment, on response to HCV treatment cannot be assessed in a vacuum. Individual and regimen characteristics have a substantial impact on treatment response, making it all the more difficult to assess the specific impact of RAVs on treatment outcomes.

Life After HCV Cure: Fibrosis Regression and Morbidity After an SVR12

HCV cure is associated with improved morbidity and mortality in those who attain an SVR12; however, a subset will still experience hepatic complications despite cure, including fibrosis progression and HCC.[11] In a Spanish cohort of HIV-infected individuals with cirrhosis who were cured of their HCV infection with DAA-based therapy, the majority showed improvement or no change in liver function at the time of SVR12, as measured by Child-–Turcotte-Pugh (CTP) or Model for End-Stage Liver Disease (MELD) score. However, a subset demonstrated worsening liver function despite HCV cure, with 8% having worsening MELD scores and 27% having worsening CTP scores (Abstract 603).

In a French cohort of 235 HIV-infected individuals successfully treated for HCV infection, hepatic complications were rare but did occur in 2 individuals who developed hepatic decompensation within the first year after cure (a rate of 3.9/1000 person-years) (Abstract 605). Focusing on 38 individuals with HCC who had been previously cured of HCV infection, 29% to 38% did not have cirrhosis, depending on the methodology used, suggesting that risk for hepatic cancer remains in some individuals despite HCV cure and may not always be associated with the presence of cirrhosis (Abstract 604). Overall, these data serve as a reminder that individuals with cirrhosis should continue to be screened for HCC even after HCV cure, as the risk for hepatic cancer may remain even if fibrosis regresses.

Data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) cohort highlighted the impact of factors known to be associated with liver disease in those with HIV infection (Abstract 150). The cohort included 34,044 HIV-infected adults, including a subset of 12,158 with at-risk alcohol use as measured at entry into the study. Adjusted population attributable risk fractions (aPAFs) were determined, taking into account the prevalence of a given risk factor along with its aHR for end-stage liver disease

(ESLD). In the entire cohort, HCV infection accounted for 33% of ESLD (aPAF), and a CD4+ cell count below 200/μL and hepatitis B virus (HBV) coinfection had aPAFs of 25% and 16%, respectively. In the subgroup for whom alcohol use data were available, the contribution of HCV infection to ESLD increased slightly to 35%, and alcohol use itself accounted for 33% of ESLD. These data support the profound positive impact widespread HCV treatment could have on ESLD incidence in those with HIV infection, with or without alcohol use.

Impact of HCV Infection Outside the Liver

Hepatitis C infection has been associated with a number of extrahepatic manifestations, including cryoglobulinemia, B-cell lymphoma, diabetes mellitus, and kidney disease.[12] Further, successful eradication of HCV can lead to improvement or resolution of these conditions.[13,14] Several abstracts examined the impact of DAA treatment on extrahepatic manifestations of HCV infection in those with HIV coinfection.

Two abstracts examined the impact of DAA therapy on diabetes. In a detailed analysis of 29 HCV–infected individuals (10 coinfected with HIV) treated with DAA drugs, levels of fasting glucose and hemoglobin A_{1C} improved rapidly during therapy (Abstract 610), with mean reductions of 53 mg/dL and 1.95%, respectively. Of 25 individuals with evaluable end point data, 6 of 25 (24%) individuals required a dose reduction of insulin or metformin. In a large-scale analysis of the Spanish AIDS Study Group (GeSIDA) cohort (SVR, n = 633; no SVR, n = 992), after controlling for other factors, an SVR following HCV treatment was associated with a reduced incidence of renal events (HR, 0.38; P = .046) and diabetes mellitus (HR, 0.56; P = .018) (Abstract 611). As expected, SVR was also associated with a decreased risk of overall and liver-related mortality.

An analysis from the Swiss HIV Cohort Study examined the impact of HCV seropositivity and HCV viremia on a number of outcomes, including renal disease and liver-related and all-cause mortality (Abstract 612). All HCV-seropositive individuals (regardless of viremia) had an increased incidence ratio for liver-related death compared with HCV-seronegative matched controls, (although viremia tended to further increase the incidence ratio). In contrast, incidence ratios for liver disease were only statistically significantly elevated in those with HCV viremia. Non–liver-related mortality was not associated with HCV seropositivity.

Frailty and low muscle mass are increasingly being evaluated as potential complications of long-standing HIV infection and premature aging. The potential contributions of viral hepatitis coinfection (HCV or HBV) to low muscle mass were evaluated in the MACS (Multicenter AIDS Cohort Study) and WHIS (Women's Interagency HIV Study) cohorts (Abstract 609). In this cross-sectional study, low muscle mass was found in 27% of coinfected participants versus 12% of HIV-infected and 10% of uninfected controls. Coinfected participants were more likely to have low muscle mass (OR, 1.94) than HIV-monoinfected participants. Among coinfected participants,

lack of HIV suppression was statistically significantly associated with low muscle mass (OR, 2.28; 95% CI, 1.11-4.66). The impact of successful HCV therapy on low muscle mass should be evaluated in future studies.

Progression of Liver Fibrosis Among Those With HIV Infection: Assessment, Pathogenesis, and Interventions

Liver Fibrosis: Assessment

Noninvasive methods for staging of liver fibrosis have largely replaced biopsy in the management of HCV infection, and staging of fibrosis is essential for obtaining health insurance approval of HCV medications in the United States. Two abstracts (Abstracts 527 and 528) compared various methods for staging of liver fibrosis in HIV/HCV-coinfected individuals. Fibrosis-4 (FIB-4) and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) scoring are readily available indices used to stage liver disease, and FibroTest (or FibroSure) is a commercially available blood test that is also used to stage liver disease in the setting of HCV infection. The variability between these 3 methods, when normalized to a 4-point scale, was assessed in the setting of the phase IV ASCEND trial of HCV treatment in a community-based setting (Abstract 528). There was consistently less variability between APRI and FIB-4 scores than between FibroTest results and FIB-4 or APRI score, which is unsurprising as these metrics rely on many of the same laboratory values (AST level, platelet count). When compared across liver disease stages, less variability between FibroTest results and FIB-4 or APRI score was observed at estimated early stage disease. The absolute values are lower, so less variability would be expected. Coinfection status did not appear to impact the variability. It is tempting to speculate that the differences correlate to a better predictive ability of one test versus the others; however, this study did not evaluate correlations to fibrosis stage as assessed by another method (eg, biopsy or transient elastography) or outcomes.

FIB-4 has been shown in cohort studies to be a good predictor of HCV liver disease–related outcomes in coinfected individuals.[15] Transient elastography is an ultrasound procedure that can be performed at the bedside and that stages liver disease based on liver stiffness; although cutoffs vary, 9.5 kPa and 12.5 kPa are often used to indicate Metavir stages 3 and 4 liver disease, respectively.[16,17] In a retrospective analysis, 1159 HIV/HCV-coinfected individuals were assessed from first transient elastography measurement until last follow-up for liver-related events (decompensation, HCC) or death (Abstract 527). Associations between outcomes were assessed, including a comparison of first FIB-4 score and liver stiffness. Liver-related events occurred in 75 participants (6.5%) over a median follow-up period of 5.8 years. Those who experienced liver-related events were more likely to ingest more than 50.0 g of alcohol per day, to have a CD4+ cell count below 350/μL, and to not have achieved an SVR with HCV therapy. Not surprisingly, death was more common in

those with liver-related events. Both baseline FIB-4 score and liver stiffness each predicted liver-related events or death: mean baseline FIB-4 scores were 3.14 and 1.24 and mean liver stiffness measurements were 26.0 kPa and 8.0 kPa for those with and without liver-related events, respectively. However, the area under the receiver operating characteristic curve (AUROC) for transient elastography as a predictor of liver-related events or death was significantly higher than for FIB-4 scoring ($P < .001$). Using cutoffs of a FIB-4 score of 3.25 or higher and a liver stiffness measurement of 9.5 kPa or higher, the aHRs for liver-related events were 5.36 (3.22-8.93) and 18.7 (9.0-38.7), respectively

A unique aspect of transient elastography is that, rather than a binary designation of cirrhosis or no cirrhosis, its values are continuous variables as liver stiffness increases from the 12.5 kPa to 14.6 kPa threshold for cirrhosis to the maximum value possible of 75.0 kPa. Merchante and colleagues from Spain presented additional data from the prospective HEPAVIR study cohort on the ability of a liver stiffness value of 21.1 kPa to differentiate individuals at risk for variceal hemorrhage (Abstract 530). The cohort consists of 488 HIV/HCV-coinfected participants, predominantly men, most taking antiretroviral therapy (92%), with a diagnosis of cirrhosis determined by a liver stiffness measurement of greater than 14.0 kPa and no prior decompensation. At entry into the study, 90% of individuals had CTP class A and 10% had CTP class B cirrhosis. Prior to 2009, all participants underwent screening for esophageal varices with esophagogastroduodenoscopy (EGD), and only those with a liver stiffness measurement greater than 21.0 kPa underwent EGD screening after 2009. The primary end point was time to first instance of variceal bleeding, with a median follow-up period of 53 months. Consistent with prior results, no participant who maintained a liver stiffness measurement of less than 21.0 kPa suffered from variceal bleeding during the follow-up period (n = 128), for a 100% negative predictive value. The probability of variceal bleeding was significantly higher in those with a baseline liver stiffness measurement of greater than 21.0 kPa ($P = .001$), and 3.2% of patients with a liver stiffness measurement of greater than 21.0 kPa experienced variceal bleeding. Six of 16 patients with variceal bleeding died. In a second study from the same group, a combination of liver stiffness measurement and CTP scoring achieved better prediction of liver decompensation events than either alone (Abstract 529). Despite this, CTP class A cirrhosis was always predictive of a lower rate of liver decompensation than was CTP class B cirrhosis; liver stiffness measurement was used to further separate risk among those within a given CTP class.

Liver Fibrosis: Pathogenesis and Interventions to Slow Progression

Liver disease remains a major cause of morbidity and mortality among those with HIV infection.[18] Although much attention continues to be focused on viral hepatitis coinfection, other factors such as fatty liver disease and HIV infection

itself are increasingly recognized as contributing to liver disease among those with HIV infection.

Despite the identification of many factors epidemiologically linked to HCV-associated liver disease progression, the ability to predict which individuals will progress and how fast the progression will be remains limited. In an analysis of the ALIVE (AIDS Linked to the Intravenous Experience) study cohort, semiannual transient elastography assessments were used to examine factors associated with the progression of liver disease and progression to cirrhosis (Abstract 548). Over 8 years of follow-up, 10% of participants progressed from having no or low fibrosis (< 8.0 kPa) to having cirrhosis (> 12.3 kPa), and as expected, moderate or severe fibrosis was associated with a higher rate of mortality. Although changes in transient elastography scores during semiannual visits effectively determined if liver disease had progressed, a high false-positive rate is likely to limit its clinical usefulness. The investigators concluded that accurate prediction of liver disease progression was imperfect and that withholding treatment from those less likely to progress was not justified.

HCV genotype 6 infection is endemic in Southeast Asia and was associated with significantly more fibrosis progression (measured by transient elastography) than genotype 1 infection (aOR, 4.02; $P = .047$) in a cohort of untreated HIV/

> *Successful treatment of HCV infection remains one of the most powerful interventions to prevent progression of liver disease in those with HIV/HCV coinfection.*

HCV-coinfected individuals in Thailand followed up for a median of 2.1 years. These data suggest that those with HCV genotype 6 infection should be prioritized for treatment in resource-constrained settings, given the risk for disease progression (Abstract 606).

Progression of liver fibrosis related to HCV infection is accelerated in those coinfected with HIV, particularly if HIV replication is not controlled.[19] However, the effects of HIV replication and CD4+ T-cell depletion on liver fibrosis progression, independent of viral hepatitis coinfection, have not been well characterized. Data on 14,198 HIV-infected participants from the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort were used to evaluate the contribution of various factors to progression of liver fibrosis measured by FIB-4 scoring (Abstract 558). Progression was defined as an increase in FIB-4 score from below 1.45 to above 3.25 (advanced fibrosis) during the follow-up period. Of participants, 1386 (9.7%) progressed to advanced fibrosis over a median of 3 years. Although classic factors such as HCV or HBV coinfection and alcohol use were associated with progression of fibrosis, HIV viral load and CD4+ cell count were also statistically significantly associated with progression of fibrosis. Increased risk for progression with higher HIV viral load or lower CD4+ cell count as well as statistically significant interaction between having an HIV

RNA level above 500 copies/mL (aHR, 1.7) and a CD4+ cell count below 200/µL (aHR, 3.3) further strengthened the findings when combined (aHR, 7.3; 95% CI, 6.4-8.3). These results lend further support to the recommendation to treat all HIV-infected individuals at diagnosis. A cohort study from Germany with smaller numbers but liver fibrosis assessed by transient elastography reported similar results (Abstract 560). In this cohort of 432 HIV-infected individuals, only 16% of whom were coinfected with HCV, uncontrolled HIV replication was associated with development of severe liver fibrosis (≥12.5 kPa; HR, 2.43; P = .034).

In a complementary study, the intrahepatic effects of HIV therapy on HCV infection were evaluated using single-cell laser microdissection to assess intrahepatic HCV RNA levels in individual hepatocytes. Specifically, Quinn and colleagues set out to determine what effect antiretroviral therapy has on the intrahepatic HCV viroscape and to identify potential effector mechanisms for any effect seen (Abstract 151). The investigators were able to show that the number of HCV RNA–containing hepatocytes correlated positively with plasma HCV viral load and that following antiretroviral therapy the number of HCV RNA–containing hepatocytes decreased. The amount of HCV RNA per cell did not seem to change with antiretroviral therapy. Intrahepatic gene expression related to type I interferons (IFI16) and antigen presentation (HLA-E, CIITA) did increase and correlated with decreases in HCV RNA set points.

Two cohort studies demonstrated the protective effect of statins on progression of liver disease. In a retrospective cohort study of HIV/HCV-coinfected individuals in the US Department of Veterans Affairs Clinical Case Registry, use of statins more than 30% of the time during the evaluable time period protected against development of cirrhosis, particularly in those with an alanine aminotransferase (ALT) level below 40 IU/L (Abstract 550).

In a study of HCV-monoinfected US veterans that examined differences between the specific statins used, atorvastatin and fluvastatin were associated with larger decreases in FIB-4 score over time compared with other statins (Abstract 551). For all statins combined, a cumulative defined daily dose (cDDD) of greater than 180 was associated with an HR of 0.6 for cirrhosis and 0.51 for HCC, indicating that longer exposure to statins was associated with a dose-dependent reduction in development of cirrhosis and liver cancer.

In another study involving statins, researchers examined the role of statins on nonalcoholic fatty liver disease—defined as a liver-to-spleen attenuation value of less than 1.0 measured by computed tomography scan—in an exploratory secondary analysis of a clinical trial that examined the impact of atorvastatin on subclinical coronary artery disease.[20] Of 40 HIV-infected individuals, 9 with nonalcoholic fatty liver disease and 28 without, 40 mg daily of atorvastatin was associated with a significant increase in liver-to-spleen attenuation ratio, suggesting a decrease in fatty liver, compared with placebo (0.46 vs -0.4, respectively; P = .03). The change in hepatosteatosis was statistically significantly correlated with decreases in low-density lipoprotein cholesterol, suggesting

and association between statin use and reduced lipid levels (Abstract 553).

A number of epidemiologic studies have noted that coffee consumption may have protective effects against the development of liver fibrosis and a variety of other conditions.[21-23] In a study from the French Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS) CO13 HEPAVIH cohort, the impact of coffee consumption on mortality was investigated in HIV/HCV-coinfected participants (Abstract 549). The study included 1035 HIV/HCV-coinfected participants

> *Epidemiologic data continue to support the protective effect of coffee consumption and statin use on progression of liver disease, including among those with HIV/HCV coinfection.*

for whom a baseline questionnaire was available and vital status was recorded for at least 1 follow-up time point. The median follow-up period was 5 years, and 77 deaths occurred of which 43% were HCV-related. Coffee consumption of 3 or more cups per day was associated with a decreased risk of death (aHR, 0.5; 95% CI, 0.3-1.0; P = .045). However, being treated for and cured of HCV infection had the most profound effect (aHR, 0.2).

IDU is the major risk factor for HCV acquisition, and HCV infection and IDU can lead to systemic immune activation, yet the relative contribution of each is poorly understood. Peripheral markers of inflammation were measured among 4 groups: 1) those actively injecting heroin, 2) those with previous IDU who had not injected heroin for 1 month to 2 months, 3) those with previous IDU who had not injected heroin for 3 months to 4 months, and 4) those who did not inject heroin. The investigators assessed the relative contributions of IDU and HCV infection (50%-60% of those who had injected heroin at some point had detectable HCV RNA) to systemic inflammation (Abstract 597). Active IDU and HCV viremia each contributed to CD4+ and CD8 T-cell activation. Levels of tumor necrosis factor–α and soluble CD14 decreased and became comparable to those observed in uninfected controls in HCV aviremic individuals who ceased injecting heroin. This shows that both IDU and HCV viremia contribute to immune activation, although more work is needed to better define their individual roles.

Two abstracts evaluated the impact of HCV DAA therapy on immune activation and intrahepatic immune response on paired liver biopsies. Using paired liver biopsies from individuals treated with sofosbuvir plus ribavirin in the SPARE study, Orr and colleagues utilized quantitative image analysis to determine changes in intrahepatic immune cells or activation (Abstract 600). The number of intrahepatic CD8 T cells decreased in all areas (parenchyma and portal) after therapy, regardless of outcome (SVR vs virologic relapse). The number of CD4+ cells also decreased but only in portal areas. Similarly, the number of activated peripheral CD4+ T cells decreased during therapy with DAA drugs, and this decrease mirrored decreases in ALT levels (Abstract 599). In this second

study, paired liver biopsies showed substantial decreases in histology activity index inflammation scores posttherapy, with one group also showing a substantial decrease in fibrosis after completion of 3 months of therapy.

Hepatitis B: Testing, Transmission, and Treatment

Hepatitis B infection is an important driver of morbidity and mortality among HIV-infected individuals worldwide. Uptake of HBV testing remains low in many African HIV clinics, with testing increasing only slightly from 10.4% in 2010 to 23% in 2012 in urban HIV clinics in 9 African countries participating in the International Epidemiologic Databases to Evaluate AIDS (IeDEA), emphasizing the importance of increasing the availability of point-of-care rapid hepatitis B surface antigen (HBsAg) tests. More than 90% of HBV-infected individuals received tenofovir-based antiretroviral therapy, which is preferred for those with HBV coinfection because of its efficacy as HBV treatment (Abstract 565).

Access to tenofovir for HBV/HIV-coinfected individuals was lower in a West African study, ranging from 15% to 61% depending on the locale (Abstract 568). In a Kenyan cohort of HIV-infected individuals, prevalence of HBsAg was 6.3% and was an independent predictor of early mortality (aHR, 1.84, for death; 95% CI, 1.3-2.6). Initiation of tenofovir-based antiretroviral therapy appeared to mitigate this risk (aHR, 1.45, for death; 95% CI, 0.0-2.2), whereas the risk of death remained statistically significantly elevated among those who

> *Tenofovir-based HIV regimens are a crucial part of optimal treatment of HIV/HBV-coinfected individuals. Lack of appropriate HBV screening and limited access to tenofovir disoproxil fumarate affect certain high-prevalence areas such as Africa.*

tested positive for HBsAg who initiated antiretroviral therapy that did not contain tenofovir (aHR, 3.32, for death; 95% CI, 1.8-6.2) (Abstract 562). Initiation of antiretroviral therapy was also associated with regression of fibrosis in a majority of HIV/HBV-coinfected individuals in Nigeria, 81% of whom initiated therapy with a tenofovir-containing regimen (Abstract 564).

In the Swiss HIV Cohort Study, the incidence of HCC increased among HIV/HBV-coinfected participants with each year not on TDF (adjusted incidence rate ratio [aIRR], 1.13; 95% CI, 1.08-1.19), and HCC incidence was highest among those not on TDF for more than 4 years (aIRR, 4.04; 95% CI, 2.1-7.77). These data emphasize the importance of tenofovir in the treatment of HIV/HBV coinfection (Abstract 566).

In sub-Saharan Africa, HBV is thought to be primarily transmitted during childhood. However, data from the Rakai Community Cohort Study demonstrated incident HBV infection in HIV-infected adults, particularly those aged 15 years to 29 years, indicating additional opportunities for vaccination beyond childhood to prevent HBV transmission (Abstract 563). Only 40% of HIV-infected children from 6 Asian countries had a history of HBV vaccination, and more

than three-quarters had no protective HBsAb, regardless of vaccination status, emphasizing the need for improved vaccine coverage and revaccination in those for whom the initial series was not effective (Abstract 860).

Several abstracts demonstrated the protective effect of HBV-active antiretroviral regimens against incident HBV infection. In the Rakai Community Cohort Study, lamivudine-based antiretroviral therapy was associated with a 76% reduced risk of HBV acquisition compared with no antiretroviral therapy (P = .001), and no new infections occurred in individuals taking a tenofovir-based antiretroviral regimen (Abstract 563). In the Swiss HIV Cohort Study, dually HBV-active antiretroviral therapy that contained tenofovir and lamivudine or emtricitabine reduced HBV incidence substantially (aHR, 0.3; 95% CI, 0.2-0.5) compared with nondually HBV-active therapy (Abstract 567). Collectively, these data emphasize the importance of vaccination and screening for HBV among HIV-infected individuals and of ensuring access to tenofovir-based antiretroviral therapy in those identified with HBV coinfection.

Hepatitis A, D, and E

Hepatitis A

Vaccination against hepatitis A virus (HAV) infection is recommended for all HIV-infected MSM as well as other high-risk populations[24]; despite this, limited data are available on immunity and compliance with vaccination recommendations. A cross-sectional analysis conducted at several time points within the Medical Monitoring Project evaluated baseline and new HAV immunity in a population of 18,095 HIV-infected individuals (Abstract 591). At baseline, 55% of the population had evidence of HAV immunity, including 57% of 8234 MSM. Over the time period evaluated, from 2009 to 2012, 15% of the population showed evidence of newly acquired HAV immunity (either documentation of vaccination or new anti-HAV antibodies not present at baseline). Of the 360 individuals with documented vaccination, factors that were associated with vaccination included younger age (18-29 years), less than 5 years since HIV diagnosis, detectable HIV viral load, and screening for sexually transmitted infections within the last 12 months. At the end of the study period, 38% of individuals lacked evidence of HAV immunity or vaccination, including 36% of HIV-infected MSM. More work is needed to improve vaccination rates in high-risk populations such as HIV-infected MSM.

Hepatitis E

Hepatitis E virus (HEV) infection is endemic in many parts of the world, including India and Africa, and is now estimated to be the leading cause of acute viral hepatitis worldwide.[25] Two studies presented at CROI 2016 examined HEV seroprevalence and HEV RNA positivity in cohorts from the United States (Abstract 593) and Uganda (Abstract 594). HEV infection is not considered endemic in the United States, and

recent studies have found a seroprevalence of 6% that appears to be decreasing.[26] In a retrospective analysis of 2919 stored plasma samples from HIV-infected men (313 samples) and women (2606 samples) from the MACS and WIHS cohorts, HEV RNA assays were performed to assess for acute or chronic HEV infection. Numerous samples were available for patients over time, and the samples were selected for testing

> *Although practitioners must still consider HEV infection among individuals with unexplained hepatitis, data from cohort studies suggest it is a rare cause of clinical hepatitis infection among those with HIV infection in the United States.*

based on "biomarkers of liver disease and immune suppression," which were not strictly defined but are assumed to be elevated ALT and AST levels and CD4+ cell counts. Only 3 of 2919 samples tested positive for HEV RNA, with 2 cases being consistent with acute, self-limited HEV infection. The third case did appear to be chronic HEV infection, with consistently detectable HEV RNA over a period of 3 years. This case was unusual, given a CD4+ cell count above 200/µL; however, there was a clear trend of decreasing CD4+ cell count over the observation period, with dips below 200/µL. Although HIV RNA levels were not reported, it seems likely this individual was not taking antiretroviral therapy and had a substantial degree of immunosuppression. Supporting the known epidemiology of HEV disease in the United States, all isolates were genotype 3a. Based on the rarity of HEV RNA detection in this cohort, the investigators concluded that widespread HEV screening is not warranted. Although rare, chronic HEV infection should still be considered in immunosuppressed individuals with unexplained transaminitis.

In a study of HEV seroprevalence from Rakai, Uganda, 500 HIV-infected individuals were tested for HEV immunoglobulin G (IgG) along with 500 uninfected age- and sex-matched controls (Abstract 593). Samples that tested positive for IgG as well as all samples from those with CD4+ cell counts below 200/µL were also tested for HEV IgM. All samples that tested positive for IgM were then tested for HEV RNA along with random samples from those who tested positive for IgG or had a CD4+ cell count below 200/µL. Overall, the seroprevalence of HEV IgG was 47% with no difference between HIV-infected and uninfected individuals. HEV seroprevalence was associated with male sex, as has been consistently described. Only 1 sample (out of 480 tested) was positive for HEV IgM. This sample was also the only one positive for HEV RNA (out of 42 tested). This study supports the known endemicity of HEV infection in Africa but further suggests that HIV positivity is not a risk factor for HEV exposure.

Hepatitis Delta

Coinfection with hepatitis delta virus (HDV) and chronic HBV infection is relatively rare in the United States but is likely underdiagnosed. HBV/HDV coinfection leads to accelerated progression of liver disease, and there are no proven effective therapies for HDV infection.[27] Case reports have suggested that prolonged HBV DNA suppression with TDF-containing treatment may have some impact on HDV RNA levels and disease course.[28] In an analysis from the Swiss HIV Cohort, 139 of 771 individuals who tested positive for HBsAg also tested positive for anti-HDV antibodies. Of these, 122 had samples available for HDV polymerase chain reaction (PCR) testing, and 73 (60%) of these samples tested positive for HDV RNA. Interestingly, 20 of the 49 individuals with negative PCR test results also had negative results on repeat anti-HDV antibody testing performed using a different test, suggesting that 15% of the original positive anti-HDV results were false positives.

Overall HDV seroprevalence was 12.8%, and 74% had a detectable HDV viral load at a median of 4.7 $\log_{10}$ copies/mL. A subset of 20 individuals with detectable HDV RNA who were taking TDF-containing antiretroviral therapy were followed for a median of 34 months. Although the mean HDV RNA level fell in the group during treatment with TDF (from 8.1 $\log_{10}$ copies/mL to 7.2 $\log_{10}$ copies/mL), only 25% experienced a reduction in HDV RNA level of more than 2 $\log_{10}$ copies/mL. HDV RNA became undetectable in 3 individuals during the follow-up period. In contrast, HBV DNA was suppressed to below 200 IU/mL in all 20 individuals. This result is unsurprising given the relatively short duration of TDF exposure and the lack of a profound impact of TDF use on HBsAg decline or loss. Novel HBV antiviral drugs that better target HBsAg production or novel HDV inhibitors may offer improved therapeutic options for HDV/HBV coinfection in the future.

All cited abstracts appear in the CROI 2016 Abstracts eBook, available online at www.CROIconference.org.

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