Invited Review

CROI 2017: Highlights of Advances in Viral Hepatitis and Liver Fibrosis

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At the 2017 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, Washington, hepatitis C virus (HCV) infection was a major focus in the context of HIV-associated liver disease. Well-tolerated direct-acting antiviral (DAA) regimens have enabled effective treatment of the populations that are hardest to cure, including those with decompensated cirrhosis, and many studies examined the impact of HCV cure on hepatitis and extrahepatic outcomes. Scaling up access to DAA, and their impact that their universal availability can have on reducing prevalence were key topics. There was much discussion of what is needed to eliminate HCV on local and global levels and a focus on ensuring that the populations hardest to reach can access treatment. Prevention of new infections and reinfection will be key to sustaining the benefits of scaled-up HCV treatment, with particular attention to populations at elevated risk for HCV reinfection, including HIV-infected men who have sex with men (MSM) as well as some HIV-uninfected MSM on preexposure prophylaxis. In the hepatitis B virus (HBV) arena, a landmark phase III trial demonstrated that tenofovir disoproxil fumarate given to HBV-infected pregnant women at week 28 of gestation, in combination with postpartum HBV vaccination and hepatitis B immunoglobulin, resulted in zero mother-to-child transmissions of HBV.

Keywords: CROI, 2017, hepatitis, HBV, HCV, treatment, direct-acting antivirals, vaccination

HCV Natural History and Markers of Clinical Fibrosis

HIV coinfection is a well-recognized factor in accelerated progression of liver disease in those with hepatitis C virus (HCV) infection, but this association has not been extensively evaluated in children with mother-to-child transmission (MTCT) of HCV with or without HIV coinfection. In a large, retrospective, multicenter cohort from Spain, liver disease progression was evaluated by transient elastography or liver biopsy in 71 HIV/HCV-coinfected and 71 HCV MTCT-infected children (Abstract 527). The HCV genotype distribution was different between the groups, with HIV/HCV-coinfected children having significantly more nongenotype 1 infections, including 23% genotype 3 HCV (compared with 7% in HCV-monoinfected children), which could impact fibrosis progression.

There was no evidence of progression of liver disease in either group through age 10 years. After 10 years, separation was noted with evidence of significantly more progression of fibrosis in the coinfected group (24% of coinfected individuals with fibrosis stage F3/F4 at age 20 years vs 6% in HCV-monoinfected individuals; $P = .012$). HCV-monoinfected infants were more frequently treated than HIV/HCV-coinfected infants (52/71 vs 22/71, respectively) and were treated at an earlier age despite evidence of slower progression of fibrosis. An explanation for why HCV-monoinfected children were treated more frequently and earlier was not provided.

Prior studies have shown that immune activation is increased in HIV/HCV-coinfected individuals compared with those with HIV or HCV infection alone. An analysis from 2 cohorts, WIHS (Women's Interagency HIV Study) and VAHH (Study of Visceral Adiposity, HIV, and HCV), sought to further characterize this association by evaluating the contributions of liver fibrosis (by transient elastography and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and microbial translocation (via I-FABP) to sCD14 levels in HIV/HCV-coinfected (n = 120), HIV-monoinfected (n = 262), HCV-monoinfected (n = 72), and noninfected (n = 170) individuals (Abstract 526). The sCD14 levels were highest in the individuals with HCV/HIV coinfection, followed by those with HIV infection alone, then those with HCV infection alone, and finally the uninfected individuals. Liver stiffness appeared to be the primary mediator of sCD14 levels in those with HCV infection alone. In both of the HIV-infected groups, microbial translocation took on a more prominent role in driving elevated sCD14 levels (although it was not the primary determinant in either group).

Data continue to support the FIB-4 index as a convenient, valuable indicator of risk for subsequent liver-related events in persons coinfected with HIV and HCV.

The Fibrosis-4 (FIB-4) score is already well validated for predicting liver-related outcomes in HCV-infected and HCV/HIV-coinfected individuals. An updated assessment from the GeSIDA cohort determined that a FIB-4 cutoff of below 1.0 is optimal for predicting an absence of liver-related events (LRE) over the ensuing 5 years (97% negative predictive value [NPV]) (Abstract 533). The hazard ratio (HR) for LRE increased for each unit rise in FIB-4; however, the difference became

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statistically significant only at a FIB-4 of 2 or higher (HR for LRE, 8.66; 95% confidence interval [CI], 2-37; $P = .004$).

HCV Treatment Outcomes: Impact of Generics and Genotype

Access to direct acting antivirals (DAAs) remains a major barrier in the United States and globally, particularly in countries like Russia, China, and others in Southeast Asia and Eastern Europe that do not have generic drug licensing agreements. A growing number of individuals in these countries are accessing generic DAAs produced in countries like India and legally imported through buyers clubs. Of 1150 individuals treated with legally imported generic sofosbuvir plus ribavirin, sofosbuvir plus ledipasvir, sofosbuvir plus daclatasvir, or sofosbuvir plus velpatasvir, sustained virologic response 12 weeks after cessation of therapy (SVR12) ranged from 91% with sofosbuvir plus ribavirin to 96% and 100% with sofosbuvir and daclatasvir and sofosbuvir and ledipasvir, respectively (full SVR12 data were not yet available). This indicates that these imported generic versions are a feasible and economical alternative for individuals who cannot access branded DAAs (Abstract 569).

Several cohorts examined the real-world efficacy of DAAs by HCV genotype. Sofosbuvir/daclatasvir with or without ribavirin was highly effective in genotype 3 HCV/HIV-coinfected patients, producing SVR12 of 97.5% in people without cirrhosis and 93% to 97% in people with cirrhosis. Sofosbuvir and ledipasvir with or without ribavirin, which is not licensed in the United States for HCV genotype 3 treatment, was associated with SVR12 of 100% in those without cirrhosis and 88% to 95% in those with cirrhosis (Abstract 572). Viral kinetics on treatment may have predictive value with these regimens in genotype 3, with no detection of HCV RNA at week 4 associated with SVR12 of 97.6%. HCV detected below the limit of quantitation associated with an SVR12 of 85.7%, and an HCV RNA level greater than the lower limit of quantitation (LLOQ) is associated with an SVR12 of 75% ($P = .001$) (Abstract 570). This association of viral kinetics on treatment with SVR12 was not seen in participants with nongenotype 3 HCV infection, and it remains to be seen if this association will hold with next-generation DAAs that may have better activity against HCV genotype 3 infection. In HCV genotype 4 infection, the real-world SVR12 rate with oral DAA regimens was high at 93%, was similar in HIV-infected and HIV-uninfected individuals, and was reduced in the presence of cirrhosis as well as unfavorable IL28B TT genotype (Abstract 571).

Toxicity and Drug Interactions During DAA Treatment

Understanding clinically significant drug-drug interactions between antiretroviral therapy and DAAs is crucial when treating HCV infection in HIV-coinfected individuals. Ledipasvir and velpatasvir each elevate plasma tenofovir levels when coadministered with tenofovir disoproxil fumarate (TDF), an interaction that has raised concern for possible renal toxicity. In HIV/HCV-coinfected patients taking TDF-based regimens, 8 weeks of ledipasvir and sofosbuvir led to a 1.9-fold increase in plasma tenofovir concentrations and a 16-fold increase in tenofovir diphosphate in red blood cells over pretreatment levels (Abstract 404). In the ION-4 study, all participants were on TDF-based antiretroviral therapy given with efavirenz, raltegravir, or rilpivirine and treated with ledipasvir and sofosbuvir (Abstract 138). An increase in proteinuria was demonstrated in 34% of participants. A small number experienced impaired renal function; 5.7% of participants had a creatinine clearance decrease of more than 25%, and 12.5% had a creatinine clearance increase of more than 0.2%. Elevated markers for renal damage (retinol binding protein and beta2 microglobulin) were present in those with impaired renal function and correlated with elevated tenofovir area under the curve (AUC), suggesting that elevated tenofovir concentrations may lead to kidney damage during ledipasvir/sofosbuvir–based therapy with TDF. However, the overall impact of ledipasvir on kidney function, including the elevation in tenofovir levels, appears to have little clinical significance in most individuals.

The HCV PI/NS5a combination of glecaprevir/pibrentasvir is expected to become available during the coming year. A noninfected volunteer study found no significant interaction between the fixed-dose combination (FDC) of dolutegravr and abacavir and lamivudine and glecaprevir/pibrentasvir (Abstract 413). Coadministration of FDC elvitegravir and cobicistat and emtricitabine and tenofovir alafenamide (TAF) led to increased elvitegravir and cobicistat concentrations (maximum plasma concentration [C_{max}], 29%-36%; AUC, 42%-47%; C_{24}, 71%-72%), as well as increased glecaprevir (AUC increased 3.1-fold, C_{24}, 4.6-fold) and increased pibrentasvir (AUC_{24} increased 57%, C_{24}, 89%). However, the authors suggest that these changes are not expected to be clinically significant based on label recommendation and exposure safety analyses from phase III data. In the EXPEDITION-2 HIV/HCV coinfection study, glecaprevir/pibrentasvir was coadministered with raltegravir, dolutegravir, rilpivirine, abacavir, TDF, and lamivudine/emtricitabine. Efavirenz and etravirine are not expected to be compatible with glecaprevir/pibrentasvir due to drug-drug interactions.

HCV Treatment in Cirrhosis and Post–Liver Transplant

One of the important benefits of current DAA therapy is the ability to more safely and effectively treat individuals with cirrhosis, including decompensated disease, than with interferon. DAA-based therapy (with more than half taking ribavirin as well) was generally well tolerated in a Spanish cohort of HIV/HCV-coinfected individuals with compensated cirrhosis, with only 1.2% stopping due to adverse events (Abstract 535). Ninety-three percent attained SVR12, which was lower among treatment-experienced individuals (88.8%) than those who were treatment naive (97.5%) ($P = .025$). Transient elastrography improved by a mean of 5.6 kPa at the time

of SVR12. It should be noted that individuals with cirrhosis are still advised to continue with hepatocellular carcinoma (HCC) screening even if noninvasive measurements suggest regression of cirrhosis. The MADRID-CoRE (Madrid Coinfection Registry) cohort evaluated outcomes of DAA treatment in HIV/HCV-coinfected individuals in clinical practice, across a spectrum of fibrosis stages, including decompensated cirrhosis (Abstract 534). Fifty-two percent received ribavirin with their all-oral DAAs. The SVR12 rate was highest among those without cirrhosis (93.5%) than those with compensated cirrhosis (91.2%) and those with decompensated cirrhosis (80.8%), which was significantly lower than those with or without compensated cirrhosis. Among individuals with decompensated cirrhosis, SVR12 rates were 86.7% for Child-Turcotte-Pugh (CTP)-A and 79% for CTP-B, and showed a significant drop-off to 44% in the most advanced disease class, CTP-C, which has been seen in other cohorts of DAA treatment in individuals with decompensated cirrhosis.

HIV-infected individuals are increasingly able to access liver transplantation. In the post–liver transplant recurrence of HCV infection, all-oral DAA therapy led to high SVR rates of 95%, which were similar in HIV-infected and HIV-uninfected individuals and is good news for those developing HCV infection posttransplant (Abstract 540). Unfortunately, HIV-infected individuals are known to experience higher rates of acute rejection after liver transplantation than their HIV-uninfected counterparts; HCV genotype 1 and mismatch in HLA-A, HLA-B, and DR alleles were all associated with increased acute rejection (Abstract 541).

DAA regimens are effective among a wide range of HIV/HCV-coinfected patients, including those with cirrhosis and post–liver transplantation.

Impact of HCV on Extrahepatic Disease, Lipid Profiles, and Overall Mortality

Chronic HCV infection is associated not only with liver disease, but also with all-cause mortality and end-organ disease such as chronic kidney disease (CKD). In a retrospective analysis performed at 2 large health organizations in Denver, the demographics of individuals who are HCV RNA positive versus those who are HCV RNA negative were evaluated, and an association between HCV RNA positivity and common comorbid conditions was assessed in new enrollees from 2008 to 2015 (Abstract 528). Not surprisingly, HCV-seropositive individuals tended to be older men within the birth cohort. They also had significantly higher rates of alcohol abuse and current tobacco use, which may confound other disease associations. Among nonliver comorbid conditions, HCV RNA positivity was associated with depression, coronary artery disease (CAD), CKD, and all-cause mortality. However, odds ratios for these conditions were significant only for depression, CAD, and all-cause mortality. Overall, low rates of HCV screening were seen in both health organizations (5.5% to 7.2%). Among individuals who are HCV RNA positive, only 11% to 17% had been treated for their HCV infection (less than 5% of the predicted population with chronic HCV infection).

Functionally, HCV could impact cardiovascular disease by contributing to endothelial dysfunction. This was evaluated cross-sectionally in a group of 45 HIV-suppressed, HCV-infected persons by measuring the reactive hyperemia index (RHI, a correlate of coronary endothelial function, with low RHI indicating endothelial dysfunction). No clear association between HCV infection or liver fibrosis stage and low RHI (indicating endothelial dysfunction) was found. Even traditional factors such as smoking, dyslipidemia, and hypertension were not significantly associated with poor endothelial function, although trends were observed. This study leaves the question open of whether or not HCV infection itself impacts endothelial function in those with HIV.

Telomere length is a marker of aging, and HIV infection has been associated with accelerated aging. The relative contribution of HCV infection and rapidity of loss of telomere length following seroconversion for either HCV or HIV has not been examined. In a cohort of injection drug users with samples available before and after seroconversion for HIV or HCV, telomere length was assessed on whole blood samples with a quantitative polymerase chain reaction (PCR) method (Abstract 590). In preseroconversion samples, persons who subsequently acquired HCV had significantly shorter telomere lengths than those who subsequently seroconverted for HIV or who were nonseroconverters. Of note, 30% of subsequent HCV seroconverters were already HIV seropositive, suggesting a likely explanation for the shorter preseroconversion telomere lengths. Following seroconversion (median 9 months postconversion) HIV individuals had the lowest relative telomere length, with a significant drop from their preseroconversion length. In contrast, no change in telomere length was seen after HCV seroconversion. Although conducted over a limited time span, these data suggest that HIV infection has more of an acute and dramatic effect on telomere length than HCV infection. Longer term follow-up would be of interest.

Several studies examined the impact of an HCV cure on lipid levels. Sofosvubir/ledipasvir treatment was associated with an increase in low-density lipoprotein (LDL) and total cholesterol during treatment that was not seen with participants treated with paritepravir/ritonavir/ombitasvir/ritonavir/dasabuvir (Abstract 573). However, after treatment completion, LDL and total cholesterol were similar regardless of the DAA treatment assignment, but with a trend toward higher levels than pretreatment. An Italian cohort also demonstrated a significant increase in total cholesterol, LDL, and oxidated LDL during a variety of DAA therapies (Abstract 575). They also noted an improvement in insulin resistance and a significant reduction in the proportion of individuals with prediabetes after an HCV cure.

In a cohort of US veterans, the risk of acute myocardial infarction was higher in HCV-infected individuals than HCV-uninfected individuals with similar lipid profiles, suggesting

that untreated HCV infection itself increases the risk for cardiovascular events (Abstract 574). Is HCV treatment beneficial or harmful to cardiovascular health?[1,2] Total cholesterol and LDL are known to be lower in HCV-infected individuals than in uninfected controls, and cirrhosis is also known to reduce lipid levels. Thus, some cholesterol increase with curative therapy may be seen as a "return to health" phenomenon rather than an increase in the risk of cardiovascular disease. These lipid effects may be counterbalanced by improved glucose metabolism and decreased inflammation, which could conversely decrease cardiovascular risk. More data are needed to understand if the DAA-induced rise in lipids has negative clinical impact on cardiovascular disease and if specific patient populations may benefit from lipid-lowering therapy during HCV treatment.

A cohort of HIV/HCV-infected individuals in Scotland reminded us of the high mortality rate in this population, particularly among those who continue to use opiates (Abstract 529). Mortality was 7.78/100 person-years and involved drug overdose in a third of the deaths. Not surprisingly, lower albumin and poor HIV disease control were associated with mortality.

Promising Future HCV Therapeutics

Broadly neutralizing antibodies (bNAbs) hold substantial promise as potential HIV therapeutics. An in vitro screen of HCV bNAb combinations identified a synergistic combination that may prove to be an effective HCV vaccine strategy (Abstract 141).

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a feared complication of cirrhosis and is more common in those with HIV coinfection. In a cohort of more than 2600 HIV/HCV-coinfected US veterans with cirrhosis, HCC occurred in 3.2% over a median of 5 years, and was associated with older age, but not with race/ethnicity, HIV suppression, or CD4+ cell count (Abstract 539).

There has been ongoing controversy about whether curative DAA therapy may lead to elevated rates of new HCC diagnosis or HCC recurrence. In a Spanish cohort study of 32 centers (GEHEP-002), the rate of new HCC cases in HIV/HCV individuals was statistically significantly increased from 9% to 16% in the era before all-oral DAA treatment to 31.7% in the all-oral DAA era ($P < .001$) (Abstract 139). The authors attributed this to increased uptake of treatment in individuals with cirrhosis, a nearly 3-fold increase, who are at higher baseline risk for HCC and may be more likely to be screened once evaluated for treatment. HCC recurrence after HCV treatment occurred in a very small number of individuals and was not significantly different in the DAA era compared with the pre-DAA era. Similarly, data from the Italian SCOLTA (Surveillance Cohort Long Term Toxicity of Antiretrovirals/Antivirals) demonstrated that the rate of HCC in individuals with cirrhosis (Metavir stage F4) during the first 16 months after DAA treatment was the same as in untreated historical controls. In those undergoing DAA treatment, cirrhosis was associated with HCC development, when compared with those with Metavir stages F0 to F3 (HR, 4.7; 95% CI, 1.08-20.44), a reminder of the importance of providing HCV treatment before advanced fibrosis develops (Abstract 542LB).

In an analysis from the GEHEP-002 cohort of 317 HCC cases among HIV/HCV-coinfected individuals, 32.5% of those with HCC who were apparent candidates for therapy did not receive treatment or received suboptimal treatment according to the tumor stage at diagnosis. No treatment or suboptimal treatment was more common at more advanced stages of HCC (Abstract 538). However, the proportion of suboptimally treated individuals declined from 43.6% before 2010 to 27.4% from 2010 to 2016, suggesting improved access to appropriate care.

Continued, lifelong screening for HCC after cure of HCV infection is crucial for individuals with cirrhosis.

HCV Screening and Diagnostics

Despite recommendations from the Centers for Disease Control and Prevention (CDC) in 2012 and the US Preventative Services Task Force (grade B recommendation) in 2013, an uptake of birth cohort HCV screening for those born between 1945 and 1965 (Baby Boomers) appears to be limited. Indeed, a study from Washington, DC, demonstrated only 12% of more than 80,000 individuals eligible for HCV screening in the birth cohort were tested when a screening prompt was built into electronic health record (EHR) clinical protocols (Abstract 545). Although in more than 50% of the cases, health care practitioners never clicked on the screening prompt, more disheartening is that when the HCV screening prompt was accessed, only 43% of individuals were subsequently screened.

The care cascade generated from those screened was typical, with large drop-offs from documentation of HCV RNA positivity to being seen in an HCV treatment clinic (53%, 80/151), and another sizeable drop-off in completing pretreatment evaluation and having a prescription for HCV therapy written (25%, 37/151). A second study with a different EHR prompt (Abstract 544) yielded more promising results, demonstrating an increase from 6.2% screened during preintervention to 38.6% during postintervention. Differences included a prompt rollout for individuals in a hospital setting as opposed to those in an outpatient clinic, and the appearance of the EHR prompt on screen instead of the need to click the prompt to view screening recommendations.

Cases of acute HCV infection have increased dramatically over the last several years and are likely underestimated. With this rise in acute HCV infection, testing of nonbirth cohort populations will need to occur more frequently. Most HCV cascade data are based on birth cohort populations predominantly. The HCV care cascade for a nonbirth cohort

population was generated from a retrospective chart review within a large health system in the Washington, DC/Maryland area (Abstract 543). Among almost 7000 nonbirth cohort individuals tested for HCV infection, 1.6% were seropositive. HCV RNA positivity was seen in only 60% of those with antibody-positive HCV infection, and advanced fibrosis stage ([F3-4]) assessed by FibroSure) was present in only 14%. In contrast to the birth cohort-based HCV epidemic in this area of the country, which is predominantly in blacks, the nonbirth cohort were predominantly white men (also presumed younger, but not specifically stated). Younger age and recent infection would also explain the higher spontaneous clearance rate and limited amount of advanced fibrosis.

The HCV care cascade needs continued attention, with a focus on approaches to improving screening and linkage to HCV care and treatment.

The remainder of the cascade was typical, with large drop-offs from documentation of RNA positivity to being seen by an HCV specialist (64%, 28/44), and to completing fibrosis staging with HCV treatment ordered (34%, 15/44). Individuals who tested antibody-positive HCV infection in this nonbirth cohort were more likely to be white, to be on Medicaid instead of private insurance, and to report drug use (Abstract 517). In those over the age of 40 using prescription opiates, the risk of antibody-positive HCV infection was elevated 11-fold. Notably, 23% of those with antibody-positive HCV infection reported no HCV infection risk factors, a reminder that testing based on risk factors will miss a proportion of those with HCV infection.

Confirming chronic HCV infection with detection of HCV RNA levels in serum or plasma is a potential stumbling block for widespread roll-out of HCV DAA treatment in resource-limited settings where DAA prices are significantly lower. A self-contained, small-volume PCR methodology with little to no processing requirements could help tackle this issue. Small-volume capillary blood (100 µL) obtained by fingerstick was compared with standard venipuncture for detection of HCV RNA levels on the Cepheid GeneXpert platform (Abstract 549). HCV RNA quantitation was approximately 0.5 log lower using fingerstick; however, no false-negative HCV RNA results were obtained when compared with venous blood. One HCV RNA–positive sample yielded a negative result with both blood sources on the platform. Genotypes 1a, 1b, 2b, 3a, and 4 were tested. Samples remained qualitatively positive for HCV RNA levels for 240 hours at room temperature in capillary tube volumes of 100 µL.

HCV Infection in Men Who Have Sex With Men

Acute HCV infection outbreaks in HIV-seropositive men who have sex with men (MSM) have been well described in several European settings. Evaluation of 80 acute HCV infections occurring in Paris from 2014 to 2016 in a population of largely MSM (81%), 93% of whom had HIV infection, demonstrated that about one-quarter were reinfections and the majority of infections were part of transmission chains (Abstract 52). The SHCS (Swiss HIV Cohort Study) screened 95% of HIV-seropositive MSM in the cohort, identifying approximately 5% with HCV RNA positivity. Of note, 17% of these were incident infections, 6 of these remained HCV antibody-negative, and 2 had normal liver function tests (Abstract 521).

A retrospective cohort of HIV-infected MSM from the University of California San Diego found a steadily rising incidence of HCV diagnoses over time, from 0.36/100 person-years in 2000 to 2003 to approximately 1.1 to 1.14 per 100 person-years in 2004 to 2011, to 1.5/100 person-years in 2012 to 2015. The authors point out that these rates are similar to those reported in London and other European cities with epidemics of acute HCV infection in HIV-seropositive MSM populations, and double the rates observed in the US MACS (US Multicenter AIDS Cohort Study). Intravenous drug and methamphetamine use were each significantly associated with a higher HCV incidence. However, 13.4% denied ever using intravenous drugs or methamphetamines, highlighting that MSM contact alone is an important route of HCV transmission, particularly in the HIV-seropositive population (Abstract 134).

The Amsterdam PreExposure Prophylaxis (AMPrEP) project reported 15 MSM who were HCV RNA–positive at the time of enrolling in a PrEP project, including one with likely acute HCV infection (HCV antibody-negative) (Abstract 519). HCV infection was associated with younger age; increased number of encounters involving receptive anal sex while not using condoms; intravenous drug use, amphetamine use, or gamma hydroxybutyrate use during sex; and a recent sexually transmitted infection (STI). The HCV infection strains were closely related to those already circulating in the HIV-infected MSM population. This is an important reminder that HCV can be sexually transmitted among MSM who are HIV-uninfected as well, and that populations on PrEP may have an increased risk for HCV infection. This merits counseling and regular testing for HCV as a potential STI.

Toward Eradication: Cohort Studies

Since November 2015, unrestricted DAA therapy has been available to all HIV/HCV-coinfected individuals in the Netherlands, leading to widespread treatment of HCV infection. In the ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort, which collects data from 95% of HIV-infected individuals in that country, 65% of HIV/HCV-coinfected individuals had been cured or were on treatment. Those who completed treatment had an impressive 98% SVR rate (Abstract 136). These data demonstrate the remarkable impact that unrestricted access to DAA can have on HCV treatment uptake and cure over a short time. During the same time, acute HCV infection in HIV-seropositive MSM decreased by 52%, with a drop in both first-time infections and reinfections, a real-world demonstration of HCV treatment as prevention (Abstract 137).

In the French Dat'AIDS cohort (16 centers with almost 33,000 individuals) HCV treatment rates among the 15% who

were coinfected were analyzed from 2012 to 2015 (Abstract 550). HCV treatment rates increased dramatically over time in all groups (men, women, treatment naive, treatment experienced, Metavir stages F0 to F2 and stages F3 to F4) and with all genotypes. The nadir in rates of HCV treatment initiation was seen in 2013 during the transition from interferon (IFN)-based therapies to DAA-based therapies. By 2015, essentially all therapy was DAA-based. With this rollout, by the end of 2015, 50% of the HIV/HCV-infected individuals in this cohort had been cured, 30% were untreated, and 8% had failed prior therapy and were (presumably) awaiting retreatment. Unfortunately, over the same period HCV incidence increased from 3.5/1000 person-years to 6.9/1000 person-years in line with other Western European countries. Predictably, the majority were HCV genotype 1a and 4, matching the known epidemiology of acute HCV infection in HIV-seropositive MSM in this area. Reinfection rates were even higher than incident infection rates (although without a consistent trend over the time analyzed) at 25.6/1000 person-years. It is hoped that with a continued focus on high levels of treatment in this population (along with counseling on prevention) a decrease in incident infection and reinfections will be realized as shown in the Netherlands.

To understand the impact of scaled-up DAA treatment on HCV prevalence in France, modeling by the Dat'AIDS cohort projected that with continued treatment coverage of 30% per year, which was the treatment rate in 2015, HCV prevalence in HIV-infected individuals would drop to 1.31% by 2021 and to 0.55% by 2026. However, due to a higher predicted acute infection and reinfection rate, high-risk MSM would need higher treatment uptake to 70% to decrease prevalence to the same degree. Importantly, with increased treatment of those with known HCV infection, undiagnosed individuals will make up a larger proportion of HCV-infected individuals who have untreated disease. This highlights the need to pair increased treatment with increasing detection and engagement in care to effectively achieve HCV eradication (Abstract 135).

Similar to the French experience, a dramatic increase in uptake of HCV treatment was seen in the Duke Medical System from 2013 to 2015 (particularly 2015) (Abstract 552). Although the majority of individuals were treated in 2015 for both HCV and HIV/HCV coinfection, only 12% of individuals infected with HCV and 17% of individuals infected with HIV/HCV had been treated by the end of 2015. Interestingly, in the DAA era there was a trend toward better SVR12 rates in the coinfected group (91% HCV infected vs 96.5% HIV/HCV coinfected, $P = .05$). Data suggested this may have been driven by differences in SVR12 rates in individuals with cirrhosis (88.2% HCV-infected individuals with cirrhosis vs 96.3% HIV/HCV-coinfected individuals with cirrhosis), although liver disease parameters were similar among groups of individuals with HIV/HCV coinfection and individuals with HCV infection and cirrhosis. Of interest, 17% of individuals with HIV/HCV coinfection modified their antiretroviral therapy to accommodate DAA treatment.

Data from HCV treatment programs in various countries suggest that with widespread, unrestricted access to DAA therapy for HCV-infected persons, incidence rates of HCV may decrease in shorter time frames than predicted.

The uptake of HCV treatment from 2013 through 2015 in several specific vulnerable populations in Canada was assessed in the CCC (Canadian Co-Infection Cohort) (Abstract 553). As in other cohorts, the uptake of treatment bottomed out in 2013 (7/100 person-years), with a slight rise in 2014, and a dramatic increase by 2015 (25/100 person-years). Vulnerable populations evaluated were active persons who inject drugs (PWID), women, and indigenous/aboriginal persons. Although lower uptake was seen in all 3 groups, in the adjusted model, indigenous (adjusted odds ratio [aOR], 0.51; 95% CI, 0.31-0.85) and active PWID (aOR, 0.58; 95% CI, 0.35-0.98) maintained significantly lower odds ratios for uptake of DAA treatment. The uptake of treatment in MSM was significantly higher (aOR 1.75; 95% CI, 1.20-2.55). Disease characteristics such as suppressed HIV viral load and advanced fibrosis were also predictive of treatment starts.

HCV Treatment in Traditionally "Harder-to-Treat" and Vulnerable Populations

Although not a consistent finding, some studies have found black race to be associated with lower response rates to DAA treatment. In a prospective cohort from 2014 to 2016, 255 consecutive HIV/HCV-coinfected individuals, in a predominantly black clinic population, were evaluated for their response to DAA treatment (Abstract 560). Demographics in the cohort were 73% men, 88% black, 69% PWID, and 57% persons with a psychiatric diagnosis. HIV RNA suppression was attained in 85%. The vast majority in the cohort (91%) were treated with a fixed-dose combination of sofosbuvir and ledipasvir. The SVR12 rate for the entire cohort was 96%, including 96% in black individuals (95% CI, 93%-98%) and 97% in nonblack individuals (95% CI, 83%-99%). Among the 9 non-SVRs, potentially significant factors included nonadherence (3), proton pump inhibitor (PPI) use (2), and inadequate (nonguideline-recommended) therapy (2). An HIV RNA level above 20 copies/mL and a recent change in antiretroviral therapy were associated with non-SVR in univariate analysis.

Another vulnerable population traditionally viewed as difficult to treat are the homeless or marginally housed. Responses to DAA therapy were assessed in this population through the Boston Health Care for the Homeless Program (Abstract 557), which used a multidisciplinary team and weekly adherence phone calls for those on therapy. Among those who completed therapy, 97% (62/64) achieved an SVR12. The 2 treatment failures were individuals with cirrhosis: 1 genotype 1 individual treated with 12 weeks of sofosbuvir/ledipasvir (no ribavirin) and 1 genotype 2 individual treated with 12 weeks of sofosbuvir plus ribavirin prior to a change in guideline recommendations.

Comorbid behavioral health conditions (mental health or substance abuse disorders) are prevalent in those with HCV infection and certainly impacted eligibility for interferon-based therapies. In the DAA era, less data are available on the impact that comorbid psychiatric conditions may have on SVR (or on uptake of treatment). In a study at a Federally Qualified Health Center (FQHC) with treatment provided by primary care practitioners, 326 individuals completed therapy from 2015 to 2016 (Abstract 556). Response rates were assessed by the presence of psychiatric conditions or substance abuse disorders. In an intent-to-treat analysis, among 70% of the treatment population who had behavioral health conditions, the SVR12 rate was 94% compared with 93% of individuals without diagnosed behavioral health issues. One limitation is that no mention of uptake rate in this group was given compared with those without behavioral health conditions.

Marginalized populations may not be able to effectively navigate the health care system to access HCV therapy. One approach is to bring HCV therapy to them (Abstract 554). At a syringe exchange program, 45 individuals were evaluated and 26 were treated on site. Among those not treated, the largest group was excluded (7) due to denial of insurance or late approval. All individuals had injected within the last month, and 58% were also on opiate substitution therapy (OST). Twenty-three completed treatment (22/23 with SVR per protocol; 22/26 overall, or 85%). There were 2 discontinuations due to dropouts (1 because of loss of insurance coverage) and 2 early relapses with a genotype switch from 1a to 3. Both early relapses had injecting risks, but each had only a single injecting partner who was not infected with genotype 3. Although reinfection seems most likely, the possibility of mixed infection at baseline should be considered.

Field delivery of HCV therapy with minimal monitoring was evaluated in Chennai, India (Abstract 559). Fifty current or former PWID were randomly assigned 1:1 with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks, or sofosbuvir plus ribavirin for 24 weeks. Injections were delivered in-clinic weekly, and directly observed therapy (DOT) of pills, which were delivered with food, was used daily. Monitoring consisted only of a monthly complete blood count. The majority of participants were genotype 3a (~80%), and 20% had cirrhosis (greater than 12.3 kPa). Most individuals (88%) completed treatment in both arms. Participants in the sofosbuvir plus peginterferon alfa and ribavirin arm had an SVR rate of 88%, and those in the sofosbuvir plus ribavirin arm had an SVR rate of 60%.

Despite intensive efforts, only 76% of sofosbuvir plus peginterferon alfa and ribavirin and 80% of sofosbuvir plus ribavirin doses were completed; achieving high rates of adherence was difficult (greater than 95% adherence in 68% of the sofosbuvir plus peginterferon alfa and ribavirin arm, and 64% of the sofosbuvir plus ribavirin arm). Interferon-based therapy appeared to be less sensitive to noncompliance or missed doses with no drop-off shown in SVR rates with decreasing levels of adherence. Ongoing substance use appeared to be a significant issue with treatment adherence and efficacy.

Limited clinical trial data with DAAs have suggested similarly high rates of SVR in individuals on OST. Data from 2 Spanish cohorts (HEPAVIR-DAA and GEHEP-MONO) further support this assertion (Abstract 555). The cohorts consisted of prior injectors (male, younger, and predominantly genotype 1a and genotype 3) both on OST and not on OST compared with persons who did not inject. Individuals on OST had significantly higher liver stiffness than those not on OST and noninjectors (21.1 kPa vs 14.1 kPa and 12.2 kPa, respectively). The percentage of individuals with cirrhosis was also higher in both PWID groups than in noninjectors (57% and 52% vs 45%, respectively). Significant differences in rates of sustained virologic response 4 weeks after cessation of therapy (SVR4) were seen across these groups following DAA therapy (interferon-free): never injected (n = 803), 95%; PWID not on OST (n = 740), 91%; and PWID on OST (n = 190), 88% ($P < .001$). However, SVR4 rates according to an observed treatment or per protocol analysis were no different among the 3 groups (differences were ascribed to higher drop-out rates in the PWID groups).

Continued follow-up from GECCO (German Hepatitis C Cohort) compared outcomes utilizing DAA therapy in 1156 HCV and 349 HCV/HIV-coinfected individuals (Abstract 551). In the cohort, HIV-seropositive individuals were more likely to be men, have genotype 4, and have higher baseline HCV RNA levels (27% vs 17%, > 6 million IU/mL). Surprisingly, cirrhosis was more prevalent in HCV-monoinfected individuals (31% vs 22%). Overall, the SVR rate (95%) was identical in HCV versus HCV/HIV-coinfected individuals (95% vs 94%). In univariate analysis, HIV-seropositive individuals with a CD4+ cell count below 350/μL or who had cirrhosis were less likely to achieve SVR. On multivariate analysis, only cirrhosis remained a significant predictor of non-SVR. This is in line with other studies that have not shown a consistent negative impact of a low CD4+ cell count on SVR12. Lower CD4+ cell counts may be a marker for portal hypertension; but when controlled for cirrhosis, the effect was lost.

Another presentation from GECCO looked at HCV reinfection rates among those who had follow-up through at least SVR4 (n = 1483) (Abstract 567). Reinfections were documented in 1.7% of participants (n = 24). All reinfections were in men (despite being only 63% of the cohort) and occurred at a mean of 41 weeks after treatment. Risk populations were PWID (21%), MSM (58%), and MSM plus PWID (21%). Eighty three percent were HIV coinfected. Consistent with prior studies, the reinfection rate in MSM (11%) was higher than that in PWID (1%).

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These data suggest that DAAs have fulfilled their promise of high efficacy and tolerability among many diverse and traditionally difficult to treat populations with HIV. Continued

work is needed on screening and rolling out DAAs in a more systematic fashion to reach populations at highest risk and those that are most marginalized, particularly if HCV treatment as prevention is to live up to its promise.

Expansion of HCV Treatment by Nonspecialists

Nonspecialist practitioners will be required to effectively treat the large number of chronically HCV-infected persons in the United States and globally. Using the Project ECHO (Extension for Community Healthcare Outcomes) model, HCV specialists at a large FQHC clinic serving a low-income population were able to dramatically increase the proportion of individuals treated for their HCV infection by primary care practitioners (PCPs) in a short period of time (Abstract 548). In a span of 1 year, PCPs went from treating 1.25% of all individuals treated for HCV infection in a given 6-month period to 60%, while the overall volume of HCV treatment increased by almost 80%. SVR12 rates were 94% in a per protocol analysis, but substantially lower by ITT (73%) because of significant loss to follow-up with missing data at the SVR12 time point.

Origins and Impact of HCV Resistance and Retreatment

Resistance-associated substitutions (RASs) at position 93 (Y93) in nonstructural protein 5A (NS5A) inhibitors are of significant clinical impact. A comprehensive in vitro assessment of Y93 position variants in genotype 1a and 1b was undertaken (Abstract 563). As expected, the impact on NS5A inhibitor susceptibility was largest in genotype 1a, with most amino acid variants conferring a greater than 100-fold shift in 50% effective concentration (EC_{50}) to all currently available NS5A inhibitors. In addition, most variants (with the exception of Y93D) were relatively fit for replication (> 10%, particularly in the presence of drugs). In genotype 1b, the impact of Y93 variants was variable, with minimal impact on elbasvir and VEL EC_{50} (less than a 10-fold shift). These data fit well with clinical observations that also suggest a limited impact of baseline NS5A RASs in genotype 1b. The impact of Y93 variants in genotype 3 was not assessed.

A retrospective NS5A sequencing analysis of 112 individuals treated with DAAs in Spain found a trend toward more frequent multiple (2 or more) baseline NS5A RASs in individuals who experienced treatment failure (18% vs 5%, P = .085) (Abstract 562).

Optimal approaches to retreatment and a better understanding of the role of resistance testing in retreatment of DAA failures is needed. A large survey of 274 DAA failure patient samples submitted for sequencing to a reference laboratory in Spain was reported, with 88% treated with NS5A inhibitor-containing regimens (Abstract 566). As expected, given that the majority had failed NS5A-based regimens, NS5A RASs were seen most frequently, either alone or in combination with NS3 RASs. Retreatment regimens were variable and the numbers too small for any one genotype and retreatment regimen to draw conclusions on optimal retreatment regimens or the impact of RASs on responses. Mixed genotype infections were found in only 2% of 255 samples evaluated by deep sequencing. Reinfections also appeared rare in this cohort.

An abstract combining results from 2 studies (GS-US-337-1746 and ACTG A5348) shed some light on retreatment approaches for individuals whose condition failed to improve with sofosbuvir therapy without an NS5A inhibitor (Abstract 568LB). In study 1746, 12 weeks of sofosbuvir/ledipasvir with or without ribavirin were given to those without cirrhosis and 12 weeks of sofosbuvir/ledipasvir with ribavirin versus 24 weeks without ribavirin were given to those with cirrhosis. In study A5348, 12 weeks of sofosbuvir/ledipasvir plus ribavirin versus 24 weeks without ribavirin were given to participants randomized by their cirrhosis status. Despite the different regimens, several clues to optimal retreatment emerged. Twelve weeks of sofosbuvir/ledipasvir without ribavirin should not be used in the retreatment of DAA failures (3 relapses, 81% [13/16] SVR). In individuals with cirrhosis, an extension of therapy to 24 weeks appears preferable to 12 weeks with ribavirin (no relapses vs 5 relapses, respectively). No treatment failures were seen in A5348 but numbers were small (7 total). Baseline NS5A and NS5B RASs did not have a clear impact. Although the results were too small for firm conclusions, overall they support the approach of both studies to extend duration to 24 weeks and adding ribavirin until well-validated next-generation regimens for retreatment of DAA failures are available, later in 2017.

HCV Immunology

Immune correlates of successful DAA therapy are difficult to identify given the high success rates of current DAA therapies. Studying less potent therapies when immune function remains with an impact on treatment outcomes may provide valuable insights. The whole blood transcriptome was analyzed and compared in individuals treated with sofosbuvir and ribavirin for 24 weeks who achieved SVR (n = 24) and relapsed (n = 16) (Abstract 586). Individuals experiencing relapse had higher baseline expression of genes associated with inhibition of the inflammatory response. At the end of therapy, those who relapsed had a higher expression of a T-cell–inhibiting gene, *PDCD1*, and a lower expression of genes involved in interferon signaling.

Mucosal-associate invariant T (MAIT) cells play an important and innate immune function, particularly to bacterial pathogens, and have been shown to be depleted early in HIV infection. Peripheral and intrahepatic MAIT cell frequencies were evaluated in controls as well as in HCV-infected and HCV/HIV-coinfected individuals with minimal and advanced fibrosis (Abstract 587). In peripheral blood, MAIT cells were depleted significantly in all groups with chronic viral infection (HCV and HIV) compared with controls. MAIT cells appeared to be relatively more depleted in those with coinfection and advanced fibrosis. MAIT cell function, as assessed by interferon gamma or granzyme B production, was significantly impaired in those with advanced fibrosis than in those with

minimal fibrosis. Intrahepatic MAIT cell frequencies were relatively preserved. Whether the decreased MAIT cell frequencies in peripheral blood account for part of the susceptibility to bacterial infections in these populations remains to be determined.

Other Hepatitides

Hepatitis B Virus

Hepatitis B virus (HBV) coinfection is an important driver of morbidity in HIV individuals around the world. In HIV/HBV-coinfected individuals initiating TDF-based antiretroviral therapy at urban sites in Zambia and in rural settings in Mozambique, the 1-year mortality rate was high at 16% and 8%, respectively (Abstract 581). Individuals had advanced HIV disease as indicated by 40%, with WHO HIV stage 3 or 4, and median CD4+ cell counts of 208/μL to 232/μL. It would have been of interest to have comparator mortality data for HIV-monoinfected counterparts.

In a phase III double-blinded trial, HBV-monoinfected pregnant Thai women who were positive for hepatitis B surface antigen (HBsAg) and who were positive for the e antigen (eAg), median HBV DNA level 8.0 $\log_{10}$ IU/mL (interquartile range [IQR], 7.1, 8.5) were randomized to receive TDF 300 mg versus placebo from 28 weeks of gestation through 2 months postpartum. All infants received HBV vaccine and hepatitis B immunoglobulin (HBIg), and were breastfed (Abstract 584LB). No transmission occurred in the mothers who were randomized to TDF, whereas 2% of infants treated with HBV vaccine and HBIg developed HBV infection, which is the lowest transmission rate that has been reported in a study of HBV-untreated mothers whose infants received vaccination and HBIg at birth. The difference was not statistically significant, as the study was not powered to detect a difference with the low transmission rate in the control arm. TDF was safe and well tolerated and represents an important tool to prevent mother-to-child transmission of HBV infection, which this study demonstrates can be brought to zero with a combination approach. Placed in context, prior data have shown that 8% to 12% of infants are HBV-infected at birth when born to HBV-infected mothers with high level viremia or who were positive for eAg, despite administration of HBV vaccination and/or HBIg.[3]

In HBV-infected mothers with a high HBV DNA level, TDF started at 28 weeks of gestation, in addition to postnatal HBV vaccine and HBIg, led to no mother-to-child transmission of HBV infection.

Hepatitis Delta

Acute hepatitis delta (HDV) infection was frequent in the 1990s in Spain, particularly in HIV-infected individuals. In a Spanish cohort of PWID, the prevalence of individuals who were positive for HBsAg dropped markedly from 35% in 1993 to 1996 to 6.4% in 2011 to 2014, with a similar decline in HDV from 30% to 4.2% during the same time periods, reflecting, at least in part, the impact of widespread HBV vaccination and implementation of successful needle exchange programs (Abstract 578). Hepatitis delta prevalence was quite high, at 40%, in individuals who were positive for HBsAg from Cameroon, placing them at a higher risk for more severe hepatitis (Abstract 577).

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Additional References Cited in Text

1. Corey KE, Kane E, Munroe C, Barlow LL, Zheng H, Chung RT. Hepatitis C virus infection and its clearance alter circulating lipids: implications for long-term follow-up. *Hepatology*. 2009;50:1030-1037.
2. Floris-Moore M, Howard AA, Lo Y, Schoenbaum EE, Arnsten JH, Klein RS. Hepatitis C infection is associated with lower lipids and high-sensitivity C-reactive protein in HIV-infected men. *AIDS Patient Care STDS*. 2007;21:479-491.
3. Wen W-H, Chang M-H, Zhao L-L, et al. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. *J Hepatol*. 2013;59(1):24-30.

