Invited Review

CROI 2019: Highlights of Viral Hepatitis

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At the 2019 Conference on Retroviruses and Opportunistic Infections (CROI), there was a major focus on hepatitis C virus (HCV) elimination and improving each component of the hepatitis C care cascade. Many interventions showed promising improvements in diagnosis and linkage to care. Settings with robust access to direct-acting antivirals (DAAs) continue to demonstrate the role of HCV treatment as prevention. However, substantial barriers to accessing curative therapy remain. Reinfection after treatment presents an important barrier to elimination, particularly in some populations of men who have sex with men (MSM). MSM without HIV infection are at an elevated risk for sexual acquisition of HCV, and several studies reported HCV rates that were as high as those seen in MSM living with HIV. There was also a focus on HCV and HBV in pregnant women. Rates of HCV infection in women of childbearing potential have increased, making prenatal diagnosis a priority. In the first study of HCV treatment during pregnancy, sofosbuvir/ledipasvir started at 28 weeks of gestation led to cure in 8 pregnant women. Hepatitis B virus (HBV)-active antiretrovirals are generally effective in suppressing HBV but have low rates of surface antigen loss despite long term treatment. Initial results from novel laboratory assessments of intrahepatic HBV viral infection events were presented, hopefully paving the way for more effective HBV treatment strategies to control and potentially cure HBV.

Keywords: CROI, 2019, hepatitis, pregnancy, HBV, HCV, acute, reinfection

Hepatitis C Virus Care Cascade

With the increasing availability of direct-acting antivirals (DAAs) and focus on HCV elimination, there is continuing attention to improving engagement along the hepatitis C virus (HCV) care cascade, particularly for the most vulnerable and difficult to access individuals living with HCV infection. Jail remains an important venue for HCV infection diagnosis with 16% of inmates at the Dallas County jail identified as HCV antibody positive on opt-out testing, 75% of whom were HCV viremic. Despite high rates (85%) of uptake of HCV education during incarceration, linkage to HCV treatment after discharge was very low (<4%) (Abstract 581). People who inject drugs (PWID) are another group highly impacted by HCV. However, PWID were less likely to engage in each step of the care cascade than non-PWID counterparts, as demonstrated in the British Columbia Hepatitis Testers Cohort (Abstract 582). Importantly, rates of sustained viral response at 12 weeks (SVR 12) were similarly high in recent PWID (91%) and never PWID (92%), renforcing that PWID can be successfully treated when able to access therapy. One effective strategy to improve diagnosis and engagement of PWID involved incentivizing PWID with HCV infection to recruit other PWID for HCV testing and linkage to care. A third of PWID were able to recruit at least 1 colleague, and this proved to be a highly impacted group, 87% of whom were HCV antibody positive (Abstract 575). Unfortunately, there was substantial drop off in those linked to HCV care and ultimately being cured. Trauma patients may also merit HCV screening, as 6.8% of trauma surgery patients at a US urban hospital were HCV RNA positive, with 19% of whom being undiagnosed at the time of surgery-based screening (Abstract 579).

Several studies evaluated intervention packages to improve engagement along the care cascade. The strategy of care facilitation, which included motivational interviewing and patient-specific needs assessment, had a modest impact in improving engagement in the steps of the HCV care cascade, with more impact seen in men receiving active facilitation than in controls (Abstract 578). Random assignment to nurse case management improved linkage to care for HIV/HCV coinfected patients (47% vs 25% without case management), but was not sufficient to impact time to treatment initiation. Overall cure rates remained low (≤5%) (Abstract 580). Leveraging non-specialists remains an important means to improve HCV uptake. In King County, Washington, a community-based approach using a combination of emergency medical responder interventions, active linkage to care, and practitioner education tripled the number of individuals tested for HCV and increased HCV treatment tenfold over 4 years (Abstract 583). Training 49 primary care practitioners in HCV care led to treatment initiation in more than 700 individuals with HCV infection, demonstrating the important role non-specialists can play in improving HCV treatment access (Abstract 587). A meta-analysis demonstrated that task shifting to non-specialist achieved similarly high cure rates of 92% compared with specialty care, in PWID and in the general population. HCV testing and treatment in non-referral settings (decentralization) led to higher uptake of HCV testing (88% vs 47%, respectively), and linkage to care (80% vs 53%, respectively), than strategies that required referral-based care (Abstract 588).

Even in settings where DAA treatment is readily available through insurance coverage, substantial barriers can

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remain for patients to access HCV treatment. An HIV/HCV coinfection cohort at an Atlanta public health hospital found 53% of HIV/HCV coinfected individuals had not been treated for HCV; the main barriers identified were alcohol and substance use (60% of those not treated) and poor HIV control (Abstract 573). Similarly, poor HIV control and well as Medicare (vs Medicaid) were associated with lack of HCV treatment in a Johns Hopkins HIV/HCV cohort (Abstract 574).

Impact of Opioid Use on HCV and Fibrosis

In vitro, fentanyl was associated with increased HIV and HCV viral replication, which provides yet another potential route by which the opioid epidemic impacts PLWH or individuals with HCV infection, or both (Abstract 618). A Miami cohort found an association of advanced fibrosis (Fibrosis-4 score [FIB-4] > 1.45) with fentanyl use (odds ratio [OR], 1.67; $P = .0035$) and HIV infection (OR, 2.25; $P=.0025$); however, it was not clear if these analyses accounted for concomitant viral hepatitis (Abstract 617).

HCV Diagnostics

HCV core antigen testing is generally a faster and less expensive alternative to HCV RNA testing to confirm HCV infection and identify acute HCV infection. When used by a London sexual health clinic, core antigen testing identified 95% of acute HCV infections. Of the 4 missed, 3 had alanine aminotransferase (ALT) levels above 300 IU/L and 1 had an ALT level 33 IU/L, leading to HCV RNA testing. Notably, using HCV antibody and ALT elevation alone would have missed 47% (37/82) of the acute HCV diagnoses (Abstract 586). Of note, HCV core antigen testing in not approved for use in the United States. The Ora-Quick rapid HCV antibody test yielded a markedly low sensitivity of 6% in HIV/HCV coinfected individuals compared with 100% in those without HIV; specificity was 100% in all groups (Abstract 584). Other groups have reported lower sensitivity of the Ora-Quick rapid HCV antibody test, particularly when shorter incubation times were used,[1] but data on performance in HIV-infected populations are limited.[2]

A simple laboratory-based assay to infer recent HCV infection would be a welcome addition to HCV epidemiologic studies. Avidity assays take advantage of the fact that antibodies produced early in the course of chronic infections, such as HIV or HCV, tend to bind less tightly to antigens than antibodies that appear later. Characteristics of a modified HCV antibody enzyme-linked immunosorbent assay (ELISA) (Genedia 3.0 HCV ELISA) were evaluated in samples from 875 seropositive individuals, including 116 with a well-defined seroconversion, being followed up in prospective cohort studies of PWID (Abstract 601). Using an avidity index (optical density ratio of dissociated well/standard assay well) of less than 40% identified samples from participants with a mean duration of infection of 113 days (range, 84-146 days) with a low false recent rate (FRR) of 0.4% (long-term infections classified as recent). Although the modified assay performed equally well for genotype 1 and 3 infections, HIV infection, particularly in individuals with CD4+ cell counts below 200/µL, was associated with a significant increase in the FRR at a 40% avidity index.

A 2-log$_{10}$ decline in HCV RNA at 4 weeks after acute HCV diagnosis was associated with spontaneous clearance ($P \leq .001$) and identified 96% of those who cleared the virus without treatment. This provides useful guidance for patients who do not want to wait up to 12 to 16 weeks to monitor for spontaneous clearance

Acute HCV and Epidemiology in High-Risk Populations

The European PROBE-C (Natural History and Treatment of Acute Hepatitis C Virus I (HCV) in HIV-positive Individuals) cohort again demonstrated low spontaneous clearance rates (12%) in acute HCV infection in PLWH (Abstract 576). Evaluation for spontaneous clearance was limited by treatment initiation during the first year after acute HCV diagnosis, which occurred at a median of 14 weeks in those taking interferon alfa (n = 277) and a median of 44 week in those taking DAAs (n = 47). Notably, a 2-log$_{10}$ decline in HCV RNA at 4 weeks after acute HCV diagnosis was significantly associated with spontaneous clearance ($P \leq .001$) and identified 96% of those who cleared the virus without treatment. This provides useful guidance for practitioners whose patients who do not want to wait up to 12 to 16 weeks to monitor for spontaneous clearance (per current American Association for the Study of Liver Diseases/Infectious Diseases Society of America [AASLD/IDSA] guidance),[3] during which time they may infect others or become lost to follow-up.

The epidemiology of incident HCV infection in HIV-negative men who have sex with men (MSM) is not well-characterized. An analysis from England examined incident HCV infection in MSM by HIV status (Abstract 598). Among 40 recent HCV infections in MSM identified from 5 clinical sites, 16 (40%) of infections were in HIV-uninfected MSM. This group was younger (34 years vs 44 years old for HIV infected), frequently on pre-exposure prophylaxis (81%), and tended to have higher risk sexual behaviors (eg, more partners, group sex, and fisting). In contrast to HIV sexual transmission, there was little awareness of the potential for HCV sexual transmission. Injection drug use was identified as a risk factor in 1 of 3 of both HIV-infected and HIV-uninfected groups. Phylogenetic analysis based on whole genome sequencing identified extensive mixing within clusters of sequences from HIV-infected and HIV-uninfected MSM.

A Thai study suggested a dramatic increase in HCV incidence among HIV

infected MSM after 2014 (0.37/100 person-years pre-2014 vs 2.21/100 person-years in 2014-2018) and was strongly associated with new syphilis infections (Abstract 599). An analysis from the HPTN (HIV Prevention Trials Network) 078 study identified a high prevalence HCV seropositivity regardless of HIV status in MSM (20% HIV infected, 16% HIV uninfected) from Boston, Baltimore, Birmingham, and Atlanta (Abstract 596). The HCV prevalence in HIV-uninfected MSM is substantially higher than prior estimates and may stem from the recruitment approach in HPTN 078, which used respondent-driven sampling to target HIV-infected MSM without viral suppression (possibly also engaging high-risk HIV-uninfected MSM).

Using a phylodynamic approach based on epidemiologic data and 213 nonstructural protein 5B gene sequences from PWID detected during chronic infection (classical group) and from MSM with or without HIV infection detected during acute infection (new group), disease transmission characteristics were estimated (basic reproduction ratio [R_o] and period of infectivity) (Abstract 594). According to the model, transmission occurs more frequently from MSM with a R_o of 2.35 (compared with 1.8 for PWID) although the period of infectivity is longer in the classical scenario (18 vs 3 months in the new group). The origin of the MSM epidemic was estimated to be in 2001.

A large phylogenetic analysis of HCV-infected PWID (n=486) from 4 cities in India demonstrated extensive clustering, with 52% of samples belonging to a cluster and large cluster sizes (mean 7.4; 6 clusters had >10 samples) (Abstract 593). Seven of 19 clusters (genetic distance <4.5% based on 5'UTR-core sequences) contained samples from multiple cities. The extensive clustering among PWID across these various cities in India suggest extensive transmission networks in a mobile population, presenting substantial challenges for harm reduction and elimination efforts.

There was an excellent symposium on acute HCV as well as the potential for an HCV preventative vaccine (Symposium S-5), which is available as webcasts at http://www.croiwebcasts.org/?link=nav&linkc=home.

HCV Treatment and Treatment as Prevention

Two abstracts focused on performance of elbasvir/grazoprevir (EBR/GZR) in diverse population outside of clinical trials. In a report looking at combined outcomes from the HEPAVIR-DAA (HIV/HCV) and GEHEP (Group for the Study of Viral Hepatitis-MONO cohorts, responses to 12 to 16 weeks (with or without ribavirin) of EBR/GZR were analyzed for 266 persons with SVR12 data available (Abstract 561). Notable aspects of the cohort included a high prevalence of PWID (53%) and HIV coinfection (27%). Consistent with registrational studies, a high SVR12 of 96% was seen and only 2.3% experienced virologic failure. Similar SVR12 data were seen in PWID (94%; $P=.43$). As has been described, numerically lower SVR12 was seen in genotype 1a (92%), although there were relatively few cases (n=64) and resistance-associated substitution (RAS) testing was not uniormly performed. If available, RAS testing is recommended in genotype 1a infection when EBR/GZR treatment is planned, as an extension of EBR/GZR to 16 weeks with the addition of ribavirin if nonstructural protein 5A RAS are detected.[4]

These cohort data support prior results demonstrating similar DAA treatment response rates outside clinical trials and in key populations such as people who inject drugs and people living with HIV

A prospective cohort from Madrid, RUA-VHC (Registry of the Use of Antiviral Agents for the Hepatitis C Virus), focused on comparing response to EBR/GZR in HIV/HCV-coinfected patients (n=134) with those with HCV monoinfection (n=1486) (Abstract 562). Notable differences at baseline between the groups included a higher prevalence of genotype 1a (37% vs 15%, respectively) and 4 (43% vs 10%, respectively) infection in coinfected participants; the prevalence of high HCV RNA and cirrhosis were similar between the groups. HIV was well controlled with 95% suppressed on antiretroviral therapy (ART) and a median CD4+ cell count of 685/uL. In unadjusted analyses, SVR12 was lower in the coinfected group (90% vs 94%, respectively; $P=.035$). The difference persisted in a modified intention-to-treat analysis excluding those lost to follow-up (94% vs 97%, respectively; $P=.029$). Although HIV infection was associated with non-SVR in a univariate analysis; after accounting for HCV genotype and cirrhosis status in a multivariate analysis the impact of HIV coinfection was lost (OR, 1.04, 0.54-2.02). These cohort data support prior results demonstrating similar DAA treatment response rates outside clinical trials and in key populations such PWID and PLWH.

Treatment as prevention of transmission is well established for HIV, and recent data from Dutch and Swiss HIV cohorts indicate this to also be an effective approach to decreasing HCV transmission in high-risk populations such as HIV-infected MSM.[5,6] An analysis presented by Garvey and colleagues from 3 large HIV clinics in London lends further support to the notion that aggressive HCV treatment can reduce incident HCV infections (Abstract 85). The study period was from June 2013 to July 2018 with data collection at 6 month intervals focusing on new HCV infections; a uniform testing approach was not used at across the sites. Incident HCV infections were split into first-time HCV infection and reinfections using standard definitions. During this time the National Health Service (NHSE) expanded access to DAAs with removal of fibrosis stage restriction in 2016. However, important limitations on access remain within the NHSE, including lack of treatment for acute infection and no DAA retreatments for reinfection.

Despite these limits, a 68% fall in all incident HCV infections (1.7/100 person-years—0.6/100 person-years) and 80% decrease in new HCV infections

(excluding reinfections; 1.5/100 person-years—0.3/100 person-years) was seen from the second half of 2015 (peak) to the first half of 2018 (last time period). However, 2 disturbing trends were noted: 1) the proportion with reinfection had been increasing in recent years (43%-47% in last 2 6-month time-periods) and 2) the overall incidence did not decline in the last 3 time periods studied (0.5-0.6/100 person-years) suggesting perhaps an underlying high-risk population without adequate treatment penetration. As has been seen in other cohorts, an increase in other sexually transmitted infections was seen over time period, suggesting decreased risk behaviors were unlikely to have contributed to the fall in new HCV infections. Decreases in time to starting treatment were seen over the study period, from a mean of 41 months in 2013 to 3 months in 2018, but relied heavily on clinical trialaccess. Reliance on treatment through clinical trials to provide key public health interventions is not sustainable and calls for a change in NHSE policies that restrict treatment for both acute and recurrent HCV infections.

A number of country-wide efforts targeting enhanced diagnosis and immediate, universal treatment of HCV in MSM with HIV infection have demonstrated dramatic short-term decreases in HCV incidence and prevalence. Although encouraging, HCV transmissions from outside the cohort could hamper elimination efforts. A phylogenetic analysis of 174 genotype 1a E1-E2 HCV sequences from HIV-infected MSM in Amsterdam attempted to determine the date of sequence introduction and further whether the introduction occurred from within the cohort or externally (Abstract 597). Ten transmis sion clusters with more than 5 sequence members were identified. The estimated dates of introduction ranged from 1993 to 2005, placing them in a similar timeframe to the French phylo dynamic data. The authors then analyzed incident infections by year and determined the ratio of new infection originating from a within transmission cluster (internal) versus outside (external). Notably the only year for which external transmissions outnumbered those from within clusters was 2018 (ratio, 1.35). Although this may be largely due to the aggressive treatment of HCV in MSM with HIV infection in Amsterdam (eliminating the pool for internal transmissions) it raises concerns for exogenous HCV reintroduction.

HCV Reinfection

The likelihood of HCV reinfection following either spontaneous clearance or after SVR12 varies based on the risk factors for initial infection. Among the major risk groups for HCV infection, PWID have traditionally been viewed as a population at high risk for reinfection. However, several European cohorts have found high HCV reinfection rates in MSM with HIV infection.[7] Few data are available from contemporaneous cohorts in the United States. Fierer and colleagues presented data from the New York Acute Hepatitis C Surveillance Network, spanning 2000 to 2018 that suggested similarly elevated rates of HCV reinfection in MSM with HIV infection (Abstract 86). The cohort consisted of 304 MSM with HIV infection who were predominantly white (82%) with a median age of 45 years. There were 845 person-years of follow-up with a median follow-up duration of 2.2 years. Thirty-eight reinfections were captured at median of 1.9 years post clearance for an incidence of 4.4 per 100 person-years, which is in the range seen in European cohorts and generally higher than seem in PWID. There was no difference in reinfection rate based on mode of prior clearance, whether spontaneous or treatment induced, although numbers are small and confidence intervals wide. In contrast, an Australian HIV/HCV observational coinfection cohort reported lower reinfection rates after cure at 0.81 per 100 person-years; of note, all 5 reinfections occurred in MSM (Abstract 577).

HCV in Pregnancy

HCV infection in pregnant women has doubled from 2009 to 2014,[8] leading to AASLD/IDSA to recommend universal HCV screening in pregnancy as of September, 2018. The American College of Obstetrics and Gynecology and US Preventive Services Task Force have not yet adopted this recommendation.

Chaillon and colleagues demonstrated that universal screening of pregnant women in the United States is cost-effective, including at the US national prevalence of 0.7%, and is even more cost effective in parts of the United States where HCV prevalence in pregnancy is as high as 8% (incremental cost-effectiveness ratio [ICER] of $5,288 at an F2 treatment threshold). Universal screening of pregnant women is anticipated to detect HCV in 33,000 US women (Abstract 589). In a retrospective evaluation of more than 10,000 preg nant women from a large mid-Atlantic healthcare system, overall HCV screening rate was 30%, and 20% of the women with HCV antibody positive test results had no reported HCV risk factor. Notably,

8 of 8 pregnant women treated with ledipasvir/sofosbuvir achieved sustained viral response at 12 weeks. Given the hepatitis B and HIV analogies, there is little doubt DAA treatment will be effective in prevention of mother-to-child transmission of HCV

there were racial disparities in screening; women undergoing testing were more likely to be African-American than white (47% vs 33%, respectively) despite a higher percentage of white women testing HCV antibody positive (71% vs 21%, respectively) (Abstract 586). These data highlight the need for more uniform guidance and uptake in HCV screening of pregnant women.

Perinatal transmission of HCV occurs in approximately 5% to 6% of births of mothers with HCV viremia, with HIV coinfection increasing this transmission rate. In one of the most anticipated hepatitis presentations at CROI, Chappell and colleagues presented the first data

of DAA-based treatment of HCV during pregnancy (Abstract 87). Extrapolating from HIV and hepatitis B virus (HBV) infection experience, it is expected that therapy that reduces the maternal viral load to zero would dramatically reduce HCV perinatal transmission.

A phase I study evaluated 12 weeks of ledipasvir/sofosbuvir for genotypes 1, 4, 5, and 6 infection in pregnant women. Key exclusions included HIV coinfection and cirrhosis. Treatment was initiated at 23 to 24 weeks of gestation with follow-up to SVR12. Infants of treated mothers are being followed up out to 1 year. Despite extensive efforts by the study team, of more than 170 HCV-infected pregnant women identified, only 29 were screened. Of those screened only 9 enrolled with 10 of 29 being excluded due genotype 2 or 3 infection, for which ledipasvir/sofosbuvir is not effective.

Not surprisingly, treatment was well tolerated (all AEs were grade 1 or 2) and efficacious with 8 of 8 (100%) of women who had completed 12 weeks of follow-up posttreatment achieving SVR12. No infant-related adverse events and no HCV transmission has been documented thus far with 5 of 9 infants having completed 1 year of follow-up. Although this is an exciting initial step, much more data are needed. The fact that 10 of 29 screened women had genotype 2 or 3 HCV infection highlights the need for futures studies with pan-genotypic regimens.

Given the HBV and HIV analogies, there is little doubt DAA treatment will be effective in prevention of mother-to-child transmission (MTCT) of HCV. However, as HCV infection can also be cured after transmission and data with DAAs is now available down to 3 years of age, the burden of proving safety is higher in HCV.

Complications of HCV

HCV and Diabetes

The benefits of HCV cure on liver-related morbidity and mortality are clear; fewer data are available on potential additional positive effects of cure on extrahepatic organ systems and HIV complications. There is a well-established epidemiologic link between HCV infection and the development of diabetes mellitus. Although few data are available on the possible beneficial effects of HCV cure on diabetes prevention and improved insulin sensitivity, several case reports have suggested a positive effect.

Using the ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans), Butt and colleagues assessed incident diabetes mellitus (DM) at more than 12 weeks after completion of HCV treatment compared with an HCV-infected untreated group propensity matched for risk factors associated with diabetes (Abstract 88). After exclusions that included HIV and prevalent diabetes, 26,000 HCV-treated veterans were compared with an equal number of controls. One-third had a body mass index above 30 and 22% had a FIB-4 score above 3.25. Of the treated veterans, 20% received an interferon alfa-containing regimen; in the DAA-treated group the most common regimen was ledipasvir/sofosbuvir with or without ribavirin (50%).

In the primary analysis, HCV group treated with DAAs (but not interferon alfa) had a significantly lower incidence rate of DM than the untreated population (9.89/1000 person-years vs 20.6/1000 person-years, respectively, $P<.0001$). A significant difference was seen (13.2 vs 19.2/1000 person-years, respectively; $P<.0001$) comparing SVR with non-SVR groups among those treated, (13.2 vs 19.2/1000 person-years, respectively; $P<.0001$). Factors strongly associated with incident diabetes included black race (hazard ratio (HR), 1.42; $P<.0001$), body mass index above 30 (HR, 3.38; $P<.0001$) and DAA treatment (HR, 0.48; $P<.0001$). Advanced fibrosis determined by a FIB-4 score above 3.25 was also associated with incident diabetes (HR, 1.29; $P<.0001$). Although observational in nature, these data strengthen the case for reduced risk of incident diabetes as an extra-hepatic benefit of HCV treatment.

HCV and Cardiovascular Disease

An analysis from the ERCHIVES cohort compared cardiovascular disease (CVD) events (assessed by ICD-9/10 codes) in HCV treated (n=32,575) vs a propensity-matched HCV untreated group of veterans without HIV (Abstract 570). By design the groups were well matched for diabetes, hypertension, and smoking status; statin use was higher in the untreated group, although the absolute difference was less than 1%. FIB-4 score was higher in the treated group at baseline, although the absolute difference was modest (1.95 and 1.70, respectively; $P<.01$). CVD disease-free survival was significantly higher in the HCV-treated group out to 36 months with curves splitting about 12 months after therapy. Curiously the benefit was seen regardless of SVR status. Fibrosis stage modulated the risk of CVD events, with more events in those with advanced fibrosis (treated 24.5/1000 person-years vs untreated 44/1000 person-years), though HCV treatment largely abrogated this effect.

Counter to the observations in ERCHIVES, an analysis focused solely on persons with HIV infection stratified by HCV exposure and treatment status found no detrimental impact of HCV coinfection, regardless of HCV treatment status, on the risk of CVD or non-AIDS associated malignancies (Abstract 565). As expected, a strong negative impact of HCV on development of liver-related complications was seen that was ameliorated by successful treatment. High rates of smoking in the cohort (~50%) and lower rates of HIV control (HIV RNA <500 copies/mL) in HCV-negative (64%) and untreated group (68% versus 90% in treated) may have confounded the results.

Although observations from ERCHIVES and other cohorts have suggested a beneficial impact of DAA therapy on cardiovascular events, mechanistic details are lacking. Proprotein convertase subtilisin-kexin type 9 (PCSK9) functions as a regulator of low-density lipoproteins (LDL) by modulating degradation of LDL-receptors on hepatocytes and inhibitors of PCSK9 form a new class of lipid lowering agents. PSCK9 has also been associated with inflammation and immune activation. Gandhi and colleagues reported the effects of DAA treatment on PCSK9 level

in HIV/HCV-coinfected persons (n=35) and compared levels over time with a well-controlled HIV-monoinfected group (n=37) (Abstract 567). At baseline LDL levels were significantly lower in those with HCV coinfection, though there was no difference in statin use. There was trend toward higher PCSK9 levels in HIV/HCV-coinfected individuals that those with HIV only (307 and 284 ng/mL; *P*=.06). A significant decrease in PCSK9 levels post-HCV treatment was seen and was modestly correlated with changes in sCD163 and sE-selectin. The significance of these associations is unclear and a causal link cannot be established at this point, particularly given the direct effects of HCV on lipid metabolism including sterol regulatory element binding protein-2, which regulates PCSK9.[9]

In a direct assessment of arterial stiffness, aortic pulse wave velocity (PWV) was measured in controls (n=27), individuals with HIV infection (n=25), with HCV infection (n=35) and with HCV/HIV coinfection (n=39) (Abstract 569). Measurements were taken before and after HCV treatment, with adjustments for age, sex, smoking, hypertension, and body mass index. No difference in PWV was seen before HCV treatment among the groups and no significant change was noted after SVR in groups with HCV. As has been noted previously, select inflammatory markers improve in HCV monoinfected patients after SVR (eg, sCD14) but HIV/HCV coinfected subjects did not show significant improvement. This study was limited by the small sizes of the groups, it is also notable that PWV is not widely accepted as a marker of CVD risk.

HCV and Renal Disease

In population-based studies HCV infection adversely impacts renal outcomes, particularly in high-risk groups such as those with diabetes mellitus. In an Italian cohort of 403 HCV-infected persons without HIV infection, including 17% with a pretreatment estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, improvements in renal function were assessed at 12 weeks or later after DAA treatment (Abstract 566). Following treatment dramatic improvements in eGFR were seen in groups with stage 3 (49.8 to 79.7; *P*<.001) and stage 4 or 5 (23.9 to 73.9; *P*<.001) chronic kidney disease (CKD). Combined the prevalence of CKD stage 3 to 5 went from 16.9% to 12.2% post-treatment (*P*<.05). Factors associated with eGFR improvement in multivariate analysis were SVR (HR, 12.2; CI, 1.26-118.11) and presence of decompensated liver disease (HR, 3.43; CI, 1.44-8.18; Child-Turcotte-Pugh score, A/B; C excluded). The specific causes of CKD were not mentioned, but the astounding improvements in eGFR in the most advanced group raise the question of whether a few cases of acute glomerulonephritis, or other severe causes of acute renal injury that are also potentially reversible, were included.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) was diagnosed at later Barcelona-Clinica Liver Cancer (BCLC) stages in HIV/HCV vs HCV monoinfected individuals (BCLC B-D in 67% vs 28%; *P*<.0001) (Abstract 609). However, HIV itself was not associated with increased mortality, in a multivariate analysis that included adjustment for HCC stage at diagnosis (Abstract 608). HCC was diagnosed within 3 months of a normal screening ultrasound in 8.6% of HIV/HCV and HCV mono-infected individuals, a reminder of the limitations of ultrasound for HCC (Abstract 609).

Another Veterans Administration cohort, the VACS (Veterans Aging Cohort Study), assessed the impact of several variables including chronic viral hepatitis, obesity, diabetes, alcohol use, and HIV infection control parameters (HIV viral load and CD4+ count) on the risk of incident HCC among an HIV-infected cohort (Abstract 90). In total, 278 incident cases of HCC were identified including 120 (43%) in veterans with a FIB-4 of 3.25 or lower, suggesting the absence of advanced fibrosis. Major factors associated with HCC were HCV RNA positivity and detectable HBV surface antigen (HBsAg). The HR for incident HCC was around 6 for HCV in both groups (FIB-4 ≤3.25 or >3.25), and HBV infection was associated with a relatively elevated risk in those with a FIB-4 score of 3.25 or lower (HR, 4.93 vs 2.12). In terms of HIV control, there was no evidence for an impact of HIV RNA level or CD4+ count on incident HCC in those with advanced fibrosis. Conversely, in the group without advanced fibrosis, both lack of HIV RNA suppression (12 or more months of HIV RNA >500 copies/mL; HR, 1.57, 1.03-2.37) and CD4+ cell count 200/µL (HR, 1.78,1.16-2.74) were associated with an increased risk of incident HCC.

Hepatitis B

Outcomes of HBV Treatment in HIV Coinfection

The goal of HBV treatment with nucleos(t)ides is HBV DNA suppression and ultimately, loss of HBsAg and immunologic control of infection with gain of HBV surface antibody (HBsAb). In a Texas cohort of HIV/HBV coinfected individuals, 96% of whom were on HBV active ART, only 10% lost HBsAg (median length of follow-up was not reported) (Abstract 624). In a similar analysis from Zambia, 10% of HIV/HBV-coinfected individuals starting tenofovir lost HBsAg over 2 years of follow-up (Abstract 625). These rates are consistent with the 5% to 15% HBsAg loss that has been described in other cohorts of ART-treated HIV/HBV-coinfected individuals. HBsAg loss was associated with lower baseline CD4+ cell count in both cohorts, greater gain in CD4+ cells (Zambian cohort), and AIDS diagnosis (Texan cohort), raising questions about the potential role of immune reconstitution potentially in HBsAg loss. However, HBsAg loss was still low in those with baseline CD4+ count below 200 cells/µL at 11% (Zambian cohort).

A German cohort of HIV/HBV-coinfected individuals on tenofovir-containing combination ART reported a similar 18% HBsAg loss over a median of 11 years (interquartile range [IQR], 10-12). HBsAg loss was less likely with low CD4+ cell gain on ART (*P*=.0043) and in contrast to the Texas cohort, less likely in presence of Centers

for Disease Control and Prevention (CDC)-C diagnosis ($P < .001$). Persistent HBV viremia despite HIV suppression on tenofovir-based ART has been described, but the etiology is not well understood. An analysis of tenofovir con centrations in dried blood spots demonstrated lower tenofovir concentrations in patients with HBV viremia and HIV suppression. This suggests that lower ART adherence may be responsible for HBV viremia and that there is a differential ART adherence threshold for suppression of HBV and HIV. No HBV drug resistance mutations were reported (Abstract 626).

HBV Reactivation and Revaccination

The US Food and Drug Administration (FDA) raised concerns about risk of HBV reactivation in those with resolved or current HBV infection during HCV treatment with DAAs with a black box warning issued in 2017.[10] A London cohort examined the risk for HBV reactivation during HCV treatment in 271 HIV/HCV-coinfected individuals taking DAAs. In 35% (96/271) HBV core antibody (HBcAb) was positive; of these 6 were HBsAg-positive, 56 had HBsAb above 10 IU/mL, and 26 had only isolated HBcAb-positive; 98% were taking at least 1 HBV-active ART medication. Of the 14 taking lamivudine as the only HBV-active ART, 2 added tenofovir and 6 started entecavir. No HBV reactivation occurred in any of the participants, including the 6 with a positive HBsAg (Abstract 628). Given the small sample size, it is not clear if the addition of tenofovir or entecavir is warranted, particularly in those without surface antigen. Overall, the lack of reactivation during HCV DAA therapy is consistent with results of a meta-analysis of HCV monoinfected individuals demonstrating no clinically significant HBV reactivation in the absence of HBsAg positivity.[11]

Optimal approaches to revaccination for HBV infection after non-response to a first series in HIV-infected persons remain unclear. A randomized trial of standard dose (20 µg) versus double dose (40 µg) Engerix-B given at 0, 1, and 6 months was carried out in HIV-infected persons on ART with preserved CD4+ cell counts (>200/µL) in Taiwan (Abstract 622). No difference was seen in the primary endpoints of anti-HBs response 10 mIU/mL or more 4 weeks after the last dose (88.2% vs 96.9% for standard and high dose, respectively; $P=.36$). However, geometric mean titers of anti-HBs were significantly higher at all time points in the double-dose group. Conclusions from these results are limited by the small study size. HBV vaccine using a novel TLR9 adjuvant (HEPLISLAV-B) has demonstrated improved antibody responses and are starting to be evaluated in HIV-infected populations.

Mother-to-child transmission of HBV can essentially be eliminated with prompt infant immunoglobulin and vaccination combined with maternal TDF

HBV in Pregnancy

The iTAP (Maternal Antiviral Prophylaxis to Prevent Perinatal Transmission of Hepatitis B Virus in Thailand) study randomly assigned HBV envelope antigen positive pregnant Thai women to receive tenofovir disoproxil fumarate (TDF) or placebo starting at 28 weeks of gestation to evaluate the impact of TDF on MTCT, with added HBV immunoglobulin and HBV vaccination provided to all infants. In an analysis of maternal HBV DNA presented at this year's CROI, 88% of women randomized to TDF had HBV DNA less than 200,000 IU/mL at delivery, a threshold that has been associated with lower risk of maternal to child HBV transmission (Abstract 629). Although 12% of women had HBV DNA levels above 200,000 IU/mL at delivery, no HBV transmission occurred from any TDF-treated mother to their infant, whereas 3 infections occurred in the placebo arm. The previously published trial was not able to demonstrate a significant benefit of TDF over infant vaccination alone, due to the unexpectedly low rate of MTCT in the vaccination/immunoglobulin-only arm.[12] However, these data are reminder that MTCT of HBV can essentially be eliminated with prompt infant immunoglobulin and vaccination combined with maternal TDF. The impact of maternal TDF on MTCT may vary depending on the specific population risk for transmission.

Another study examined the impact of maternal HBV infection on birth outcomes in an older study (HPTN 046) evaluating nevirapine to prevent MTCT of HIV in sub-Saharan Africa. A total of 88 (4.3%) of mothers with HIV infection were HBsAg positive, 10 of whom had high HBV DNA (>106 IU/mL). More than 80% of mothers were on HIV medications; however, 48% were on ART that did not contain lamivudine, and none were on TDF-based ART. Infants born to mothers with HIV infection who had high HBV DNA levels were more likely to have low birth weight (30%) than those without HBV (10%) or with low HBV DNA (6%) ($P=.04$), and HBV viremia appeared to have a dose-responsive relationship to low birth weight. High HBV DNA level was also associated with MTCT of HIV in 2 of 10 infants. These data suggest that reduction of maternal HBV DNA level may have benefits beyond maternal health and reduction of infant infection, but this has to be tempered by a small number of mother-infant pairs, particularly in the group with high HBV DNA levels. (Abstract 41LB)

Intrahepatic Evaluation of HCV and HBV

Two studies used the novel technique of single cell laser capture microdissection (scLCD) to examine viral- and immune-based phenomena at the hepatocyte level in 1) chronic HCV infection early during DAA treatment (Abstract 89) and 2) chronic HBV infection (Abstract 91). In a sub-study of A5329 that evaluated paritaprevir/ritonavir/ombitasvir plus dasabuvir (PrOD) therapy for genotype 1 HCV infection, paired liver biopsy specimens (immediately before and after 1 week of therapy) from 5 HIV-coinfected participants

were evaluated by scLCD for intracellular HCV RNA, interferon-stimulated gene (ISG) expression, and drug levels. Detailed plasma viral kinetics and drug levels were collected concomitantly. All participants had similar HCV (treatment-naive, genotype 1a HCV infection, and without cirrhosis) and HIV (HIV RNA suppressed <40 copies/mL on ART with CD4 cell count >250/µL) parameters; 2 participants were women. As expected, plasma HCV RNA showed a rapid and profound decline (-3 $\log_{10}$ copies/mL) over the first 24 hours followed by a slower decline over the next 6 days (-0.2 $\log_{10}$ copies/mL). Intrahepatic HCV RNA characteristics mirrored, or perhaps more accurately, predicted plasma observations. Before therapy the percentage of HCV-infected hepatocytes was highly correlated with the baseline plasma viral load level (Spearman r, 0.9). Roughly 25% of hepatocytes were infected before treatment (range, 7.4-42.9%) with 8 IU of HCV RNA per cell (IQR, 4-17). Interestingly during therapy the number of infected hepatocytes declined dramatically (1% infected at day 7); however, the amount of HCV RNA per cell did not change (12 IU/cell at day 7; IQR 5-27). A minority of cells at both time points contained more than 100 IU/cell.

Extrapolating intrahepatic HCV RNA expressing cell loss over the course of therapy allowed the investigators to estimate that all infected hepatocytes would be gone or cleared between 5 and 8 weeks of therapy in this small sample. All 4 participants with the second biopsy at day 7 (1 participant's second biopsy was substantially delayed) attained a SVR, so there was no opportunity to compare early intrahepatic phenomena at the cellular level between cure and viral relapse. Global intrahepatic ISG level fell in tandem with HCV RNA level. Although DAA concentrations were variable, liver concentrations (ng/g) mirrored peak plasma concentrations (ng/mL) with evidence of intrahepatic concentration particularly for protease inhibitors.

Chronic HBV infection is unique and characterized by the presence of covalently closed circular DNA (cccDNA) in infected cells that, even under suppressive nucleoside-based therapy, serves as a latent reservoir of infection. As novel treatment approaches aimed at HBV cure are advanced, a better characterization of intrahepatic HBV expression is needed. In particular, immune-based therapies aimed at eradicating infected hepatocytes will presumably require active HBV transcription for detection. Liver biopsies from 5 HIV/HBV coinfected persons were studied using scLCD and assays for HBV pregenomic RNA (pgRNA), cccDNA, and total HBV DNA via digital droplet PCR. Three of the 5 biopsies were obtained from persons on TDF-based ART and included 1 person with an undetectable HBV DNA level. In contrast to HCV, in the absence of antiviral therapy, nearly all hepatocytes (>95%) had evidence of HBV infection; in the setting of long-term TDF-based therapy this decreased to around 30%. In the samples from persons with a HBV DNA level above 100 IU/mL in plasma, HBV transcription, as assessed by HBV pgRNA, was present in nearly all cells analyzed. Conversely, when plasma HBV DNA level was below 100 IU/mL, the ratio of transcriptionally active cells to total cells with cccDNA was below 10 and significantly lower than samples from non-suppressed persons. Prolonged HBV suppression, in this case about 7 years, was associated with substantially less cccDNA per cell; 4% to 5% of all hepatocytes analyzed in these 2 samples still harbored HBV that was transcriptionally silent (no pgRNA but with cccDNA).

Hepatitis A

Recent outbreaks of hepatitis A virus (HAV) have been reported in several populations including MSM with HIV infection.[13,14] Response to a single HAV vaccine dose in a cohort of 73 patients with HIV infection (93% MSM) was suboptimal at 60% 3 months after vaccination (Abstract 620). Vaccine non-response was associated with a low CD4+/CD8+ cell ratio, but not absolute CD4+ cell count, in a multivariate analysis. Loss of protective HAV immunity over time may also contribute and was examined in a HIV clinic cohort (Abstract 621). Twenty patients had clear evidence of loss of HAV immunity; 15 with documented vaccination and 5 with prior positive antibody titers. Although CD4+ cell count was relatively preserved (mean, 376 ±85/µL) only 50% had an undetectable HIV RNA. Although not currently recommended in the United States, consideration of routine booster HAV vaccination may be warranted for certain high-risk populations.

Liver Inflammation, Nonalcoholic Fatty Liver Disease, and Nonalcoholic Steatohepatitis

In an observational AIDS Clinical Trials Group (ACTG) study analysis, one third of PLWH without viral hepatitis or heavy alcohol use had elevated aspartate aminotransferase or ALT level on more than one occasion. This transaminitis was associated with traditional risk factors for nonalcoholic fatty liver disease (NALFD) (elevated triglyceride level, high blood pressure, female sex) and had a higher hepatitis steatosis index suggesting NALFD, although imaging was not available to confirm fatty liver disease (Abstract 616)

A Copenhagen observational cohort found a lower risk for computerized tomography-diagnosed fatty liver disease (which could include alcohol-associated disease as well as NAFLD) in PLWH than in matched controls without HIV (8.5% vs 17.4%, respectively; $P<.001$). PLWH with fatty liver had typical risk factors (elevated body mass index, diabetes, alcohol use), as well as cumulative exposure time to zidovudine (adjusted OR, 1.23) despite a mean time of 9.4 years since discontinuation (Abstract 615).

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