Invited Review

CROI 2018: Highlights of Viral Hepatitis

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

At the 2018 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. Several countries and cohorts have demonstrated the remarkable impact that universal HCV testing and unrestricted access to hepatitis C treatment can have on markedly reducing incident HCV infections and HCV infection prevalence, including in people who inject drugs and HIV/HCV-coinfected populations. However, in many settings, substantial barriers to widespread HCV treatment remain, including undiagnosed HCV infection, particularly in populations outside the standard "baby boomer" birth cohort (ie, born 1945-1965); restricted access to hepatitis C treatment in those with known HCV infection; reinfection with HCV; and migration of HCV-infected populations. Many innovative programs have successfully implemented HCV testing and treatment outside of traditional care settings, expanding access for harder-to-reach populations, which will be crucial to successful elimination efforts. Outbreaks of hepatitis A virus (HAV) infection continue to occur in among men who have sex with men and homeless populations in the United States, Europe, and Southeast Asia, highlighting the need for improved HAV vaccination programs for populations at risk.

Keywords: HIV, CROI, 2018, hepatitis, HAV, HCV, prevention, testing, elimination

The HCV Care Cascade: On the Road to Elimination?

Hepatitis C virus (HCV) drug development has slowed and approvals for all current direct-acting antiviral (DAA) regimens have been in place for some time. The time has come to redouble efforts surrounding HCV diagnosis and treatment, as the prospect of HCV elimination becomes real. To that end, a number of abstracts examined where different communities and populations stand along the hepatitis C care cascade.

Early in the HCV care cascade, it is crucial to obtain HCV RNA confirmation for seropositive persons, as approximately 25% of persons may clear HCV infection spontaneously. Coinfection with HIV may hamper spontaneous clearance of HCV infection, although to what degree remains a matter of debate. Data from the PROBE-C (Prospective Observational Evaluation of the Natural History and Treatment of Acute HCV in HIV-Positive Individuals) study cohort assessed the rate of spontaneous HCV clearance in 464 HIV-seropositive participants with acute HCV infection (in this case, defined as HCV infection within the last 12 months) (Abstract 129). The cohort consisted almost entirely (98%) of HIV-infected men, with sex with men as their HCV transmission risk factor. Their HIV infection was well controlled, and more than 90% of participants had a plasma HIV RNA level below 200 copies/mL on antiretroviral therapy (ART). The HCV genotype distributions were 74% with genotype 1a and 18% with genotype 4, reflective of the genotypes currently circulating in men who have sex with men (MSM) in Europe. The spontaneous HCV clearance rate was 12%, and mean time to undetectable HCV RNA was 13 weeks (interquartile ratio, 12-18). The mean time to HCV treatment initiation was 11 weeks in participants with persistent viremia, raising the possibility that some may have initiated treatment prior to what would have been a spontaneous clearance. The only factor in multivariate analysis that was predictive of spontaneous HCV clearance was a greater than 2 $\log_{10}$ IV/mL decrease in HCV RNA level over the first 4 weeks (odds ratio [OR], >1115 [225-5515]; $P \leq .001$), which occurred in 14% of the entire cohort and 96% of those with spontaneous clearance.

Direct detection of HCV RNA allows for more prompt identification of infection, an important first step to reducing HCV transmission and linking to HCV care. Incident HCV was detectable a median 2 months earlier with an HCV antigen test and with HCV RNA testing (either standard laboratory-based RNA assay or rapid HCV PCR), than with standard HCV antibody (Ab) testing, in MSM undergoing routine screening in the IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) study (Abstract 585). Of note, only 3 of 12 MSM had elevated levels of aspartate aminotransferase at the time of demonstrable HCV viremia, serving as a reminder that early and presumably infectious HCV can be present in the absence of transaminitis.

Low rates of HCV diagnosis, the first step in the HCV care cascade, remain a major barrier to HCV elimination in the United States. In Massachusetts, one-third of individuals diagnosed with HCV infection as part of a universal screening program were unaware of their infection, highlighting that testing remains a substantial stumbling block in the HCV care cascade (Abstract 577). Emergency department (ED)-based HCV testing is a strategy to identify undiagnosed HCV-infected persons or those who remain unlinked to care. An ED HCV testing program in Baltimore, Maryland, identified 446

Dr Luetkemeyer is Associate Professor at the University of California San Francisco. Dr Wyles is Chief of the Infectious Diseases Division at Denver Health Medical Center in Denver, Colorado. Send correspondence to Anne F. Luetkemeyer, MD, 995 Potrero Ave, Box 0874, San Francisco, CA 94110. Received on March 26, 2018; accepted April 9, 2018.

ED patients with active HCV infection, 86% of whom were not in care (Abstract 578). Unfortunately, less than half of the patients were successfully linked to care, and half of those already had advanced fibrosis (Metavir score, F3 or F4). The ED holds promise as a place in which to identify chronic HCV-infected persons in need of care, but there remain substantial missed opportunities to subsequently engage and cure such individuals.

Two abstracts reported on statewide data or programs. Massachusetts has had a robust laboratory testing–based HCV monitoring system in place for years. Leveraging this data-reporting system, Vo and colleagues reported on the HCV care cascade in their state from 2007 to 2015 (Abstract 595). To generate the care cascade, investigators took confirmed HCV Ab–positive tests and then followed their laboratory progression through: 1) HCV RNA confirmation; 2) repeated (>1) HCV RNA or genotype testing in the same year as a marker for engagement in care; 3) specific testing for HCV genotype to indicate intent to treat; and 4) a negative HCV RNA test result at least 12 weeks after genotyping as a surrogate for a sustained virologic response 12 weeks after cessation of treatment (SVR12). Although there are limitations to this approach, it is a reasonable way to assess HCV care cascade parameters on a population level. Notable findings included that most of the population was outside the 1945 to 1965 birth cohort, including 45% who were younger than 40 years, and more than two-thirds resided outside the Boston metropolitan area. These are trends in a changing HCV infection epidemiology that have been seen throughout the United States, largely attributed to growing opioid epidemic.[1] Progression through the HCV care cascade continued to demonstrate several shortcomings: 1) confirmatory HCV RNA testing was only documented for 62%; 2) of those with confirmed detectable HCV RNA, a genotype was recorded for only 39%; and 3) only 2.2% had subsequently undetectable HCV RNA suggesting SVR. Of note, SVR assessment was limited because negative HCV testing results were not reported until 2015. However, it is unlikely that a substantial proportion of this population initiated and completed treatment and follow-up before 2015. The SVR rate may also be falsely inflated, given the likely inclusion of some spontaneous clearances. Hopefully, many of these individuals have been treated in the last 2 years, but much still needs to be done regarding linkage to and retention in HCV care as well as treatment.

The ACTIVE-C (Alabama Coalition for Testing, Interventions and Engagement in Hepatitis C Care) collaborative group presented results on the impact of this program, which included on-site coordinators and education, on HCV testing rates, linkage to care, and treatment since its launch in July 2015 (Abstract 594). Partners in this program include University of Alabama at Birmingham, the Alabama Public Health Department, and community health centers, which combined covered 7 cities and more than 40 clinics across Alabama. The data showed an alarming 11% HCV seroprevalence rate among more than 84,000 HCV Ab screening tests. In community clinics, large increases in the proportions of individuals completing confirmatory testing (ie, HCV RNA) were seen from year 1 (19%) to year 2 (69%) of the program. In aggregate, 29% of individuals initiated HCV treatment, with no difference between community and academic sites. The community clinic population was more likely to be black and have no insurance or Medicaid and less likely to have cirrhosis. Rates of SVR were high (95%-97%) and not statistically different between academic and community sites. Expanding HCV care beyond specialized practitioners and clinics will be essential and is feasible, as demonstrated in the ACTIVE-C collaboration.

In a somewhat similar approach within a large federally qualified health center in San Diego, California, Rojas and colleagues presented updated data on a project to empower primary care practitioners to treat hepatitis C under the guidance of a specialized team consisting of an infectious diseases physician and patient navigators working in conjunction with primary care physicians and nurse practitioners (Abstract 599). Since the project's inception in 2013, the volume of treatment grew steadily, with a shift in treatment from specialists to primary care physicians. To date, 830 patients have been treated in the program, and primary care physicians treated the majority in the last year. Per-protocol SVR12 rate was extremely high (97%), with no difference by treater. A substantial number of individuals had missing data or were lost to follow-up, making the intention-to-treat SVR12 rate only 72%. Of the 13 individuals with documented virologic failure, 11 had cirrhosis. Data from ACTIVE-C and the San Diego project demonstrate a principle initially demonstrated by the ECHO (Extension for Community Healthcare Outcomes) model: the substantial strides that can be made by empowering primary care practitioners in nonacademic settings to treat HCV infection, with excellent results.[2]

Data on the HCV treatment cascade among HIV/HCV-coinfected individuals in HIVRN (HIV Research Network) sites in the United States were presented. Radwan and colleagues compiled HCV testing and diagnosis rates across 12 HIV clinics and examined DAA treatment outcomes for 9 of 12 sites with on-site HCV treatment programs over 2 years (January 2014-December 2015) (Abstract 597). Of more than 28,000 persons with HIV infection, 79% were screened for HCV and 31% were HCV seropositive. HIV-infected persons more likely to be screened for HCV were younger than 40 years, black, or had a history of injection drug use. In contrast, among those who were HCV-Ab positive, older than 40 years of age, Hispanic race and injection drug use were associated with HCV seropositivity. High rates of HCV treatment (85% among persons with detectable HCV RNA) and SVR (96%) were observed in the subset of 9 sites with on-site treatment programs. These data are encouraging, given that they largely occurred before the widespread approval of potent DAA regimens, although the (the off-label DAA combination of sofosbuvir plus simeprevir was possible. The high treatment uptake early in the DAA era may also may reflect the inclusion of academic centers with HCV treatment on-site.

Impact of Unrestricted HCV Treatment on HCV Elimination

The Swiss HIV Cohort Study examined the impact of a comprehensive population-based approach to HCV elimination in HIV-infected MSM (Abstract 81LB). To that end, the Swiss HCVree study systematically tested 3722 MSM, a majority of the larger study cohort, for HCV infection. Of those tested, 177 (4.8%) had active HCV infection and 31 (18%) were judged to be new infections based on prior HCV test results. Of the 177 persons with HCV infection, 61 (91%) were treated with co-formulated (/) elbasvir/grazoprevir (provide by manufacturer) or with other locally provided DAAs if there was a contraindication to elbasvir/grazoprevir; 99.5% attained an SVR12. Testing for HCV was then repeated among the initially tested cohort, and 28 (0.8%) active HCV infections were identified, 16 (57%) of which were incident infections, and the remainder were those who had not been initially treated. Of the 28 HCV-infected individuals, 22 accepted HCV treatment; 100% of these achieved an SVR12. Thus, systematic HCV screening and treatment led to a 49.0% reduction in incident HCV infections and a 92.5% decrease in chronic HCV infections. This study demonstrates the remarkable impact that systematic universal testing and treatment can have on the HCV epidemic, in a setting where there are no barriers to screening or treatment. New infections from outside Switzerland may jeopardize this microelimination strategy (see Molecular Epidemiology of HCV Networks and Resistance-Associated Substitutions section below)

Several country-wide programs have now demonstrated the powerful effect universal HCV testing and treatment programs can have, in a short period, on HCV prevalence and incidence.

Spain implemented a strategy of unrestricted access to HCV DAAs. In a large Spanish HIV/HCV-coinfected "real world" cohort with a high prevalence of injection drug use (87%), 65% initiated DAA therapy, and 94.8% of those with evaluable results attained an SVR12, demonstrating the potential of universal DAA access including populations of persons who inject drugs (PWID) (Abstract 603).

Widespread DAA access in the Netherlands was associated with high SVR12 rates and a marked 51% decline in acute HCV infections in HIV-infected MSM in data presented at CROI 2017.[3] In contrast, in the French Dat'AIDS study cohort, despite high HCV treatment uptake and cure rates, the incidence of acute HCV infection in HIV-infected MSM substantially increased from 2012 to 2016 for both initial infection and for reinfection. Reinfection risk was consistently elevated over risk of first infection (Abstract 591). Of note, acute HCV incidence in HIV-infected PWID also increased but remained lower than in MSM. The reason for the differential rates of acute HCV infection in France versus Switzerland and the Netherlands is unclear but highlights the need for robust HCV reinfection counseling and surveillance to accompanying widespread DAA rollout.

In the Austrian HIV Cohort Study, remarkably high rates of screening (96%; 5364/5613) and HCV RNA confirmatory testing (99%; 1178/1195) were reported from 2014 to 2017 (Abstract 596). However, due to restrictions limiting DAA prescribing to hepatologists in 3 of the 8 HIV clinics examined, comparisons in progress along the treatment cascade were made between sites without (n = 3) and with (n = 5) prescribing restrictions. Unsurprisingly, a higher proportion of participants were treated at clinics in which in-house DAA treatment was allowed (76%) versus required referral to a hepatologist (56%). In multivariate analysis, the only factor predicting DAA treatment was availability in the HIV clinic (OR, 3.36; CI, 2.16-5.24). Higher rates of prescription of interferon-alfa-based treatment by hepatologists is not clearly explained but may have to do with a time bias: more patients were referred to hepatology in the earlier period of the study when DAAs were less available. Although the investigators state that Austria is on route to elimination of HCV disease, these data do not compare well with data from other countries in Europe or even from some HIV clinics in the United States, highlighting the adverse impact practitioner restrictions can have on DAA rollout and progress toward elimination of HCV disease.

In the United States, restricted access to DAAs remains a substantial barrier to HCV treatment. An evaluation of DAA prescriptions from 45 US states found 35% were denied, with the denial rate increasing significantly over the period studied (from 27.7% to 43.8%) (Abstract 600). Denials we more common with commercial insurance (52.4%) versus Medicaid (34.5%) and Medicare (14.7%)

Sexual Transmission of HCV and Risk for HCV Reinfection

HCV reinfection is the Achilles heel of HCV elimination efforts, with reinfection rates in HIV-infected MSM as high as 25% reported in some European settings.[4] In the French Dat'AIDS study cohort, there was an equivalent incidence of acute HCV infection in HIV-infected MSM (1.38/100 person-years) and HIV-uninfected MSM taking preexposure prophylaxis (PrEP), serving as a important reminder that MSM sexual transmission of HCV is not limited to MSM with HIV infection (Abstract 590). Data from Philadelphia, Pennsylvania, showed that younger MSM as well as heterosexual people with HIV infection may be at elevated risk of recent HCV infection via sexual transmission (Abstract 593). Prevalence of HCV infection in men initiating PrEP in New York, New York, was low at 0.26%, which is lower than in the general population (Abstract 592). However, it is clear that PrEP users remain at risk for acquisition of HCV and other sexually transmitted infections. In the GECCO (German Hepatitis C Cohort) study, the HCV reinfection rate in HIV-infected MSM was 14.3 per 100 person-years, substantially higher than the 1.8 per 100 person-years in PWID (Abstract 612). Median time to HCV reinfection was 63 weeks.

Sexual transmission of HCV is more common in those with preexisting HIV infection. One potential hypothesis for this increased risk was presented by Dutch researchers who examined HCV transmission via Langerhans cells, which are known to be present in the anal mucosa (Abstract 588). Immature cells did not transmit HCV to hepatocytes in vitro; however, exposure to HIV was associated with a substantial increase in HCV transmission to liver cells (Abstract 588).

Molecular Epidemiology of HCV Networks and Resistance-Associated Substitutions

Data using HIV phylogenetics have demonstrated the utility of sequence analysis to determine transmission pairs, including transmissions not identified by traditional epidemiologic investigations.[5] Similar data are now emerging for HCV and were presented in 2 abstracts. Data from the UFO (U Find Out) study in San Francisco, California (Abstract 584), a prospective cohort of young HCV-serodiscordant PWID in active injecting relationships, identified 40 partnerships (56 individuals) with documented new HCV infection during follow-up. Using deep sequencing of core nonstructural protein 2 (NS2) and NS5B regions, transmission clusters were identified, and interestingly, more than half of transmissions occurred outside of the primary injecting partnership, including 3 transmission events between persons not identified in an injecting relationship. Minor variant transmissions, which would only be detected by deep sequencing, were identified in at least 3 instances.

A phylogenetic analysis from the ALIVE (AIDS Linked to the Intravenous Experience) study cohort in Baltimore assessed core/E1 sequences in viremic participants from the last study visit (Abstract 581). A less than 4% difference in sequence between participants was considered a linkage in the analysis, which was limited to persons with HCV genotype 1. As expected for this cohort, most participants were black (87%) with HCV genotype 1a infection (83%). Most of the samples analyzed were from 2016 (71%). Although most participants were not in an identified cluster (68% of participants with genotype 1a, and 60% of participants with genotype 1b), 25% belonged to clusters, including 2 large clusters of participants with genotype 1a of 42 and 66 participants, respectively. Factors associated with belonging to a cluster in multivariate analysis included young age, HIV infection, and hazardous alcohol use.

Two abstracts used HCV phylogenetic data to assess large-scale transmission patterns for HCV and develop messages concerning HCV control and elimination efforts and the need for coordination. Within the Swiss HIV Cohort study, whole genome sequencing was carried out on 66 incident genotype 1a HCV infections in MSM from 2012 to 2016 (Abstract 130). The NS5B sequences from these infections were compared with sequences retrieved from public databases to attempt to ascertain the likely origin of the infecting strain. Although most transmissions appeared to originate from other HCV-infected Swiss persons, 14% to 44% (depending on the percentage of Swiss sequences in a cluster required to consider it Swiss overall) appeared to be the result of transmission from sequences originating outside Switzerland, mostly from Germany, the Netherlands, or the United Kingdom. Only 5% to 10% of sequences originating outside Switzerland came from outside Europe. The major limitation of these data is the bias imposed by using sequences uploaded to public databases, which may not accurately represent the circulating viruses in neighboring countries, leading to an underestimation of non-Swiss transmission events.

A similar investigation took sequences from collaborating sites across Europe (not available in public databases; n = 1729)) as well as those reported to public databases (n = 2740) and compared the phylogenies from NS3 and NS5A over time to assess longer-term HCV transmission trends (Abstract 582). Investigators found phylogenetic evidence for extensive HCV sequence movement between European countries, with a major signal for seeding of US sequences into Europe, primarily through jumps into Germany and Italy (although there was evidence of spread from the United States to most European countries). Despite the extensive seeding, no signal for seeding of NS5A resistance-associated substitutions (RASs) was found. As described previously, the NS3 Q80K variant was highly prevalent in North American sequences and its appearance in European sequences could be traced to introduction from North America.

The implications of these abstracts are that the positive impact of localized (even at a country level) test-and-treat strategies to control or eliminate HCV may be severely hampered by international HCV transmissions and that coordinated elimination efforts are needed on a continental or even international level.

The impact of NS5A RASs on HCV treatment outcomes is limited in most settings with currently available, highly potent DAA regimens and often requires other negative predictors to see a meaningful adverse treatment effect (e.g., treatment experience and cirrhosis).[6] In a retrospective analysis of 388 HCV genotype 1–infected DAA treatment–naive individuals, population-based sequencing was used to assess factors associated with NS5A RASs by genotype (1a vs 1b), including the Y93H variant (Abstract 583). The prevalence of NS5A RASs was similar to what has previously been described, with differences in specific mutations and prevalence by genotype 1 subtype (RASs in 6% of individuals with genotype 1a and 10% with genotype 1b). The Y93H variant was only found in sequences of individuals with genotype 1b who were DAA treatment naive. In univariate analysis, severeal factors were found to have associations with the presence of NS5A RASs (P = .05). Factors identified included older age, more advanced fibrosis, lack of HIV infection, and hepatitis B core antigen immunoglobulin G (IgG) positivity. However, correction for multiple comparisons was not made nor was a multivariate analysis undertaken (likely due to the relatively small number with RASs). A simple explanation may be time: with a longer time of infection, more random mutations in the virus are accumulated, which could result in RASs. This could explain the associations with both older age and advanced fibrosis, both surrogates for longer duration of infection. Another possible

explanation is that there is some selective pressure, possibly immune, for RASs, including Y93H. Previous data have associated the Y93H variant in persons with HCV genotype 1b infection with the iIL28B CC genotype,[7] while other data have associated the IL28B CC genotype with more rapid progression of fibrosis.[8] The IL28B genotype was not reported in the study referenced above and could be another unmeasured variable explaining the observed association. Ultimately, the small number of individuals with RASs, numerous comparisons, and lack of multivariate analysis make it impossible to judge if any of the identified associations are meaningful. Although interesting, further study in larger data sets is needed. The one clear conclusion based on the phylogenetic data from this study is that RASs are selected during viral evolution within an individual and not yet transmitted in clusters.

HCV Treatment

Compared with prior CROI conferences, relatively few data were presented on new HCV treatment regimens or approaches. Results have been mixed in terms of the benefit of treating acute HCV infection with shortened durations of therapy with DAAs.[9,10] Boerekamps and colleagues presented interim data from the ongoing DAHHS-2 study (Dutch Acute Hepatitis C in HIV Study), which is evaluating 8 weeks of treatment with elbasvir/grazoprevir in MSM with acute (<6-month estimated duration of infection) HCV genotype 1 or 4 infection (Abstract 128). Exclusions included cirrhosis, a plasma HIV RNA level above 400 copies/mL on ART, or a CD4+ cell count below 500/µL not on ART. Of the 80 participants who initiated treatment, all were MSM, 91% were HIV infected and on ART, and 24% were being treated for HCV reinfection. The majority had genotype 1a infection (64%), and the remainder (36%) had genotype 4 infection. Data on SVR12 were available for 63 of the 80 participants, and the SVR12 rate was 98% (62/63), which included 3 documented reinfections determined by phylogenetic analysis that were counted as SVRs. There was only 1 viral relapse. This study represents the largest to date using a truncated DAA treatment regimen for acute HCV infection with excellent SVR12 results. The high proportion being treated for a reinfection and early occurrence of 3 reinfections after treatment highlight the work that remains to be done on harm reduction and prevention of HCV reinfection among MSM.

Glecaprevir/pibrentasvir was recently approved for HCV treatment and has a broad 8-week length of treatment indication and a high barrier to resistance.[11] In clinical trials, this regimen failed in approximately 2% of individuals, and we do not yet have a proven retreatment strategy. Although sofosbuvir/velpatasvir/voxilaprevir has shown high efficacy in retreatment, no individuals whose treatment with glecaprevir/pibrentasvir failed were included in these studies.[12]

Interim results from an ongoing phase IIIb study of individuals whose treatment with glecaprevir/pibrentasvir failed who were retreated with sofosbuvir plus glecaprevir/pibrentasvir with ribavirin for 12 or 16 weeks were presented (Abstract 127). Participants were assigned to 12 weeks of this combination treatment if they were not infected with genotype 3, did not have cirrhosis, and had not been treated with an HIV NS5A inhibitor or NS3 inhibitor prior to failed treatment with glecaprevir/pibrentasvir. All other participants were assigned to 16 weeks of treatment. Data were presented on 23 participants: 2 treated for 12 weeks and 21 treated for 16 weeks. Genotype 3 was most prevalent (14/23) followed by genotype 1a (6/23), 7 participants had cirrhosis, and all participants had either NS5A RASs (78%) or NS3 plus NS5A RASs (22%) prior to retreatment. Both individuals with genotype 2 who were treated for 12 weeks and 20 of the 21 individuals treated for 16 weeks attained an SVR12 for an overall SVR rate of 96%. The lone viral relapse was a 67-year-old man with genotype 1a infection and cirrhosis whose prior treatments with ledipasvir/sofosbuvir and then glecaprevir/pibrentasvir for 12 weeks failed and who had the Q30K and Y93H NS5A RASs prior to treatment in the current study. The high SVR rate, even with the very limited number, sug gest this is a viable retreatment approach for individuals whose treatment with glecaprevir/pibrentasvir fails. Given the very limited number of treatment failures observed in clinical trials, it is unlikely enough additional patients could be studied to determine if ribavirin is needed or the optimal duration.

Data continue to accumulate showing that populations "less-than-ideal" as candidates for HCV therapy can achieve high SVR rates with DAA therapy, including those who actively use injection drugs or alcohol.

HCV Treatment in People Who Inject Drugs and With Alcohol Use Disorder

Concern for HCV reinfection due to ongoing sexual risk behaviors or injection drug use can be a barrier to practitioners offering HCV treatment. Interestingly, HIV-seronegative individuals with a history of injection drug use demonstrated substantially lower HIV risk-taking behavior scores after the start HCV treatment, particularly those who started both PrEP and buprenorphine (Abstract 589). As HIV risk-taking behaviors can also increase risk for HCV acquisition, these data suggest a decline in risk for HIV infection and potentially HCV infection, at least during the initial months of HCV treatment

In a cohort of HIV/HCV-coinfected PWID, heavy alcohol use was common, with 26% reporting heavy drinking and 33% with an alcohol biomarker indicating heavy alcohol use (Abstract 605). Despite this, HCV therapy resulted in a 91% SVR rate, and no markers of heavy alcohol use were associated with failure to initiate therapy or to achieve HCV cure. These data support current guidelines, which prioritize HCV treatment for those who use alcohol, including those with alcohol use disorder.

HCV in Incarcerated Populations

The incarcerated population is at high risk for HCV infection. Most data have focused on prison populations with HCV seroprevalence rates ranging from 20% to 40%.[13] Jail populations are more challenging, given the transient nature of these populations in the setting of a poorly integrated system with a lack of widespread or consensus approaches to disease screening. In a project centered in the Dallas, Texas County Jail opt-out HIV and HCV screening was offered from April to November 2017, with blood drawn for confirmatory testing and patient navigator support for linkage to care and follow-up after release from jail (Abstract 598). Of 4260 persons screened during the study period, 16.5% were seropositive for HCV. Confirmatory testing was completed in 79%, and 85% of those positive for HCV RNA received HCV education. Most cases of HCV infection (57%) were outside the 1945 to 1965 birth cohort. Of those with chronic infection (HCV RNA positive), injection drug use was the single most common risk factor (39%) and most did not have insurance (86%). Perhaps most interestingly, of 116 HCV RNA–positive persons released to the community, 69 were called, 18 were contacted, and 8 were scheduled for evaluation. Most either could not be reached, did not have a phone, or did not return messages. These data highlight the huge opportunity for HCV screening in this high-risk population and the profound challenges in follow-up and linkage to HCV care.

Complications of HCV Infection and Impact of HCV Cure

Chronic HCV infection is associated with an increased risk of liver disease as well as some extrahepatic complications, including diabetes, renal disease, neurocognitive impairment, and lymphoproliferative disease, which may improve with HCV treatment. Perhaps because of improvement in hepatic and extrahepatic comorbidities, DAA treatment was associated with decreases in inpatient and outpatient health care utilization by 21% and 41%, respectively (Abstract 611).

Porphyria cutana tarda is a common skin manifestation of HCV infection. A small Spanish study demonstrated resolution of porphyria cutana tarda in 12 of 13 individuals after HCV cure (Abstract 634). In HIV-infected MSM in the MACS cohort, HCV cure was associated with normalization of most inflammatory biomarkers except for several immune activation markers (interferon-γ, interleukin 10 [IL-10], C-X-C motif chemokine ligand 13 [CXCL13], and soluble IL 6 receptor [sIL6R]) (Abstract 635). The reason for the persistent elevation of these proinflammatory biomarkers compared with HCV-uninfected men is unclear, although one hypothesis is that inflammatory markers may be residual HCV infection in peripheral blood mononuclear cells (PBMCs), which has not been showed to lead to HCV relapse. A pilot study demonstrated a low level of HCV RNA present in PBMCs and plasma in 33% of HCV-monoinfected and 58% of HIV/HCV-coinfected individuals a median of 13 months after attaining an SVR, and investigators postulate that this may contribute to systemic inflammation (Abstract 636)

In a Spanish study of HIV/HCV-coinfected individuals, HCV cure led to an increase in low-density lipoprotein (LDL) cholesterol (and thus an increase in 10-year Framingham cardiovascular risk score) 2 years after treatment initiation (Abstract 631). However, there was no change in carotid intima-media thickness or carotid-femoral pulse wave velocity, each biomarkers of cardiovascular disease. Cardiovascular events were not reported, although this group has previously reported a trend towards an increase in the risk of cardiovascular events after HCV cure.[14] Of note, some published studies have shown a decrease in subclinical and clinical cardiovascular disease after HCV cure.[15,16]

Data continue to demonstrate positive effects of HCV treatment outside the liver and to reduce overall healthcare utilization. Though LDL cholesterol tends to increase after HCV cure, thus far there is no evidence that increased LDL cholesterol in this specific setting is detrimental to cardiovascular health.

Impact of HIV Infection on HCV Treatment

In DAA clinical trials, HIV/HCV-coinfected individuals have generally attained similar cure rates to those of HIV-monoinfected individuals. In the more "real-world" setting of the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort of HIV/HCV-coinfected individuals, SVR12 rate was high at 98.2% (Abstract 610). In contrast, a Spanish analysis found a slightly lower cure rate of 91% in HIV/HCV-coinfected individuals treated with 12 weeks of ledipasvir/sofosbuvir than in their HIV-monoinfected counterparts (97%), a finding that was maintained when restricted to those with HCV RNA levels below 6 million IU/mL. There was no difference in SVR rate between coinfected and monoinfected individuals treated with 8 weeks of ledipasvir/sofosbuvir (94.0% and 96.6%, respectively) (Abstract 607). Factors associated with lower SVR rates in HIV/HCV coinfection include low CD4+ cell count (OR for HCV treatment failure, 5.2, for CD4+ cell counts <200/μL) (Abstract 608), detectable pretreatment HIV RNA (Abstract 610), and active psychiatric illness (OR for treatment failure, 2.7) (Abstract 609).

MicroRNA: Big Applications for Small RNAs

The field of microRNAs (miRNAs) and their impact on chronic viral hepatitis and liver disease is still in its infancy, with the best studied being the unique association between miR-122 and its beneficial effects on HCV replication and prevention of HCV RNA degradation. In a session dedicated to miRNAs, early studies of novel miRNAs were presented, with most studies being associative at this point and further

work needed to define pathophysiologic relationships and mechanisms.

In the only miRNA study to deal specifically with HCV, Kith and colleagues examined global miRNA profiles in PBMCs collected from persons with chronic HCV (n = 32), spontaneously resolved HCV (n = 32), and never HCV–infected controls (n = 32) (Abstract 640); each group had the same number of men and women. In the comparison of miRNAs expression between groups, no miRNAs were significantly differentially expressed between those with chronic infection and resolved infection. In contrast, the same 19 miRNAs were significantly differentially expressed (fold change >2) when comparing never HCV–infected controls with those with resolved or chronic infection. In a pathway analysis, the investigators noted that these 19 miRNAs are associated with pathways involved in fatty acid metabolism as well as myeloid leukemia and estrogen signaling pathways. The investigators suggest that these differences represent a signature left over from prior HCV infection that persists and is similar to those with active infection.

Another abstract focused on different HIV-infected populations with liver disease, including HCV infection, nodular regenerative hyperplasia, or otherwise uncharacterized elevated alanine aminotransferase (ALT), and compared the plasma miRNA signature to uninfected volunteers and HCV-monoinfected controls (Abstract 639). Although some miRNAs appeared to be upregulated (at least 2-fold) in those with HIV or HCV infection compared with uninfected volunteers, 2 groups were examined for further characterization of miRNA upregulation; 1) participants with HIV/HCV coinfection who had minimal fibrosis at initial sampling but showed rapid progression of fibrosis, and 2), HIV-infected participants with normal ALT levels to those with elevated ALT levels or focal nodular hyperplasia. Among the 9 participants with rapid progression of fibrosis, miR-99a-5p and miR-100-5p were substantially upregulated, and levels of expression correlated with ALT and fibrosis levels (kPa, as assessed by elastography). In the HIV-monoinfected group, 2 different miRNAs were substantially upregulated and correlated with ALT and levels of fibrosis: miR-122-3p and miR-193b-5p. Much more work remains to be done before these miRNAs can be considered markers for individuals at risk for progression of fibrosis or otherwise used as biomarkers.

Two abstracts focused on miRNAs in hepatitis B virus (HBV)-infected persons. Meissner and colleagues examined miRNA signatures in persons chronically infected with HBV who were treated with tenofovir disoproxil fumarate (TDF) for 240 weeks (Abstract 637). The investigators separated their analysis based on whether or not participants had regression of liver fibrosis during treatment (n = 14), and looked for changes in miRNA expression that correlated with regression of fibrosis. The investigators also compared changes in miRNA with changes in CXCL10 and sCD163. During therapy, CXCL10 and sCD163 declined but no correlation with regression of fibrosis was found. At baseline, the expression of 2 miRNAs (miR-421 and miR-454-3p) was lower in participants that subsequently experienced regression of fibrosis. A set of 13 miRNAs had differential changes in expression over the course of treatment, with increased expression at week 240 from baseline in those with regression of fibrosis. Although further validation is needed, many of these miRNAs were in pathways dealing with stellate cell activation and fibrogenesis, suggesting biologic plausibility.

Onorato and colleagues specifically examined hsa-miR-125a-5p (Abstract 638), which was previously shown to inhibit expression of HBV surface antigen. Liver biopsy samples from consecutively enrolled participants (n = 64) with chronic HBV infection were analyzed for expression of hsa-miR-125a-5p, fibrosis stage, and expression of HBV DNA. Liver biopsies of an additional 10 participants with hepatocellular carcinoma (HCC) and cirrhosis related to HBV but negative serum surface antigen (occult HBV infection) were also analyzed. Intrahepatic expression of hsa-miR-125a-5p increased substantially with fibrosis stage. Conversely, there was a trend toward lower levels of intrahepatic DNA in participants with cirrhosis, although this was not statistically significant. Only an association between hsa-miR-125a-5p and fibrosis stage was observed; much more study is needed to determine if there is a causal link.

In HIV/HBV-coinfected persons with cirrhosis, a number of serum miRNAs changed after initiation treatment with tenofovir disoproxil fumarate and were correlated with biopsy-proven fibrosis regression, suggesting the potential for development of these miRNAs as biomarkers for fibrosis regression (Abstract 637).

Other Viral Hepatitides: Hepatitis A, B, and E and Human Pegivirus 2

Hepatitis A Virus

Outbreaks of hepatitis A virus (HAV) in at-risk populations with poor vaccination rates continue to occur, including a large outbreak in San Diego, California, primarily among the homeless population. Another major at-risk population for HAV infection are MSM, and 2 abstracts examined transmission of HAV among MSM in France and Thailand, showing that an identical strain is circulating in both populations.

In France, 51 cases of acute HAV infection were described and phylogenetically compared to the 2 strains of HAV genotype IA (IA VRD 521 2016 and IA RIVM HAV16-090) currently associated with cases in MSM across Europe (Abstract 625). From December 2016 to September 2017, 61% of the 51 cases of acute HAV infection were among MSM, and 42% of those MSM were coinfected with HIV. Phylogenetic analysis was completed for approximately 75% of cases, and all viruses belonged to 1 of the 2 circulating strains (the majority were identified as strain IA VRD 521 2016).

A cluster of 5 cases of acute HAV infection occurred in Bangkok, Thailand (Abstract 626), an area in which the last HAV outbreak was described in 2002. Among the 5 cases, 4 were in MSM and strain typing showed 3 of the 4 were identical to the European outbreak strain IA RIVM HAV16-090. The fourth case was very closely related to the same strain,

as was a fifth case in an HIV-uninfected woman in Bangkok (99.7% similarity).

These abstracts highlight the potential for intercontinental transmission of HAV among MSM (an outbreak has also been described in Taiwan) and for redoubled efforts to encourage HAV vaccination in all MSM.

Hepatitis B Virus

Hepatitis B infection is an important driver of comorbidity in the context of HIV disease. Risk factors for HCC and end-stage liver disease in HIV/HBV coinfection include less time with HIV RNA suppression, more baseline fibrosis, and lower CD4+ cell count (Abstract 620). Hepatitis delta virus (HDV) exacerbates liver disease in HIV/HBV coinfection, with HDV antibodies associated with an increased risk of cirrhosis, HCC, and death, despite the use of HBV-active ART (Abstract 622).

Hepatitis E Virus

Hepatitis E virus (HEV) infection may be spread by fecal-oral transmission as well as consumption of undercooked meat or seafood. A high prevalence of seropositivity for HEV has been described in areas of France. Mo and colleagues prospectively assessed rates of HEV seropositivity (IgG and IgM) in HIV-infected persons presenting to a single clinic in Southwestern France over 7 months (Abstract 627). Among 307 HIV-infected persons studied, 72% were men and 21% (n = 64) had evidence of HEV infection. A breakdown between IgG and IgM HEV positivity was not provided, although no persons had detectable HEV RNA by polymerase chain reaction (PCR) testing (performed in those who were positive for IgM). Although HEV seropositivity was statistically significantly associated with higher ALT levels than in the HEV-negative group, the difference was not clinically meaningful (mean ALT, 40 vs 46). No association was found with HEV seropositivity and dietary habits, in contrast to studies in HIV-uninfected – populations in France. The strongest association for HEV seropositivity was withpast or current syphilis infection (positive venereal disease research laboratory [VDRL] test result; OR, 3.79; $P = .002$; positive Treponema pallidum hemagglutination assay [TPHA] result; OR, 2.84; $P = .05$). These data reinforce the concept that HEV transmission in MSM is likely related to sexual practices but is of limited clinical significance.

Human Pegivirus

Human pegivirus (HPgV; formally known as GB virus C) has similar modes of transmission to both HIV and HCV and has been shown to slow HIV progression to a modest extent. Whether these effects are HIV clade specific is unknown and was examined in an abstract that focused on HPgV infection in HIV-infected persons in Chennai, India (Abstract 629). In 154 HIV-infected men tested, 23% were coinfected with HPgV and no differences were found in baseline HIV viral load or current CD4+ cell count in those with or without detectable HPgV RNA. When the subgroup of persons currently taking ART was analyzed, a significantly higher CD4+ cell count was noted in those with HPgV infection ($P = 0.013$; exact number of CD4+ cells not given but was approximately 580/µL vs 375cells/µL). The HPgV-infected group was younger, but baseline CD4+ cell counts were not presented to determine if there was a difference in baseline CD4+ cell count.

In a surveillance study of HCV and HPgV in more than 12,000 samples from Cameroon, a relatively low HCV RNA positivity rate of 2.47% was found. The population was mostly young (71% aged 18-40 years) and female (70%), with HIV-seronegative (n = 7628) and -seropositive (n = 4741) samples. Among samples with HCV infection, 40% also had HIV infection and 15% had evidence of HPgV infection (positive for HPgV antibodies). Interestingly, HCV infection was more revalent in persons older than 40 years (9%), and HPgV seropositivity skewed toward a younger population (15.6% in those <40 years of age vs 11.3% in those >60 years of age) seroprevalence below 40), and 11.3% seroprevalence above 60). Sequences of 5 HPgV viremic samples out of 18 tested showed a greater than 90% genetic relatedness to HPgV circulating on other continents.

It is crucial that practitioners remember that care of the HCV-infected patient with cirrhosis does not end at cure. Variceal screening and HCC surveillance are crucial and must continue after HCV cure.

Steatosis and Cirrhosis

Fatty liver disease is increasing worldwide, including in individuals with HIV infection. Among HIV-infected individuals, the presence of nonalcoholic fatty liver disease (detected by imaging or biopsy) was independently associated with cardiovascular disease and adverse cardiometabolic profiles (Abstract 642). Appropriate screening is important to avoid complications of cirrhosis, which include varices and HCC. HIV-infected individuals with cirrhosis were significantly less likely to undergo appropriate screening with esophagogastroduodenoscopy for esophageal varices than HIV-uninfected counterparts (22.7% vs 87.4%) (Abstract 645).

All cited abstracts appear in the CROI 2017 Abstracts eBook, available online at www.CROIconference.org

Financial affiliations for the past 12 months: Dr Luetkemeyer has received research grants awarded to her institution from AbbVie, Gilead Sciences, Inc, Merck and Proteus, and had travel paid for by Merck. Dr Wyles has received research grants awarded to his institution from AbbVie, Gilead Sciences, Inc, Merck, and Tacere, and has served as a consultant or advisor to AbbVie, Gilead Sciences, Inc, and Merck.

Additional References Cited in Text

1. Zibbell JE, Asher AK, Patel RC, et al. Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014. *Am J Public Health*. 2018;108(2):175-181.
2. Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med*. 2011;364(23):2199-2207.
3. Boerekamps A, van den Berk G, Lauw F, et al. Substantial decline in acute HCV infections among Dutch HIV+MSM after DAA roll out. 24th Conference on Retrovirus and Opportunistic Infection. 2-16-2017; Seattle, Washington.
4. Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. *J Hepatol*. 2017;66(2):282-287.
5. Little SJ, Kosakovsky Pond SL, Anderson CM, et al. Using HIV networks to inform real time prevention interventions. *PLoS One*. 2014; 9(6):e98443.
6. Wyles DL, Luetkemeyer AF. Understanding Hepatitis C Virus Drug Resistance: Clinical Implications for Current and Future Regimens. Top Antivir Med. 2017;25(3):103-109.
7. Itakura J, Kurosaki M, Takada H, et al. Naturally occurring, resistance-associated hepatitis C virus NS5A variants are linked to interleukin-28B genotype and are sensitive to interferon-based therapy. *Hepatol Res*. 2015;45(10):E115-E121.
8. Noureddin M, Wright EC, Alter HJ, et al. Association of IL28B genotype with fibrosis progression and clinical outcomes in patients with chronic hepatitis C: a longitudinal analysis. *Hepatology*. 2013; 58(5):1548-1557.
9. Naggie S, Marks KM, Hughes M, et al. Sofosbuvir Plus Ribavirin Without Interferon for Treatment of Acute Hepatitis C Virus Infection in HIV-1-Infected Individuals: SWIFT-C. *Clin Infect Dis*. 2017; 64(8):1035-1042.
10. Rockstroh JK, Bhagani S, Hyland RH, et al. Ledipasvir-sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. *Lancet Gastroenterol Hepatol*. 2017;2(5):347-353.
11. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection. *N Engl J Med*. 2018; 378(4):354-369.
12. Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med*. 2017;376(22):2134-2146.
13. Spaulding AS, Kim AY, Harzke AJ, et al. Impact of new therapeutics for hepatitis C virus infection in incarcerated populations. *Top Antivir Med*. 2013;21(1):27-35.
14. Berenguer J, Rodriguez-Castellano E, Carrero A, et al. Eradication of hepatitis C virus and non-liver-related non-acquired immune deficiency syndrome-related events in human immunodeficiency virus/hepatitis C virus coinfection. *Hepatology*. 2017;66(2):344-356.
15. Babiker A, Jeudy J, Kligerman S, Khambaty M, Shah A, Bagchi S. Risk of Cardiovascular Disease Due to Chronic Hepatitis C Infection: A Review. *J Clin Transl Hepatol*. 2017;5(4):343-362.
16. van der Meer AJ, Berenguer M. Reversion of disease manifestations after HCV eradication. *J Hepatol*. 2016;65(1 Suppl):S95-S108.

Top Antivir Med. 2018;26(1):30-38 .