Invited Review

CROI 2021: Viral Hepatitis and Other Forms of Liver Injury Impacting People with HIV

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At the 2021 Conference on Retroviruses and Opportunistic Infections, there was a focus on progress toward hepatitis C virus (HCV) microelimination in geographic regions and targeted populations. HCV elimination is facilitated by well-tolerated, highly effective HCV treatment that requires essentially no on-treatment monitoring in most patients, as highlighted by the MINMON (Minimal Monitoring Study or A5360) study, and that should be increasingly available to children with new data supporting feasible treatment in younger patients. Challenges to HCV elimination include HCV reinfection via sexual exposure in men who have sex with men (MSM) and continued barriers to diagnosis and access to HCV treatment. Hepatitis B virus (HBV) suppression may take years in HIV/HBV-coinfected patients. This may have important consequences as the risk for hepatocellular carcinoma was associated in a dose-dependent manner with HBV viral load and was lowest in those with sustained undetectable HBV, highlighting the need for HBV DNA monitoring during therapy. Public health programs should prioritize improving hepatitis A and hepatitis B vaccination in at-risk populations, including people with HIV, as vaccinations rates for these preventable diseases continue to be suboptimal in many settings. Fatty liver disease, heavy alcohol use, antiretroviral therapy, and COVID-19 infection were also examined as drivers of hepatic disease in HIV infection.

Keywords: CROI, 2021, hepatitis, HAV, HBV, HCV, hepatocellular carcinoma, acute, reinfection, steatosis

Hepatitis C Virus Elimination

Hepatitis C virus (HCV) elimination was in the spotlight at this year's Conference on Retroviruses and Opportunistic Infections (CROI) with encouraging progress in some populations and setbacks due to reinfection add lack of access in others. The "Focus on the Liver" symposium (Symposium 11) included an overview of US and global HCV elimination progress. In an examination of the European HCV care cascade in people with HIV, the EuroSIDA cohort reported 90% ever tested for HCV antibody (Ab), with 24% with active infection by HCV RNA, with highest prevalence in Central Eastern Europe (45%) and Estonia (62%). Sixty-five percent of those diagnosed had ever been treated, and 48% of those diagnosed were cured. Access to HCV treatment varied widely by region, from a high of 87% of those infected with curative treatment in Austria down to 6.7% in Belarus. Although most European countries met the World Health Organization (WHO) goal of 90% diagnosis in people with HIV, no region exceeded 80% HCV treatment in those diagnosed, indicating increased treatment access is needed to meet WHO 2030 elimination targets (Abstract 443). Of European Union countries, Spain has made some of the most substantial progress toward elimination in men who have sex with men (MSM). In a Spanish nationwide seroprevalence survey, HCV RNA positivity declined markedly from 22.1% in 2015 to 2.2% in 2019. This was attributed to widely available HCV treatment since 2017 with high uptake, demonstrating the feasibility of elimination in a targeted population. Of note, nearly a quarter had HCV-associated cirrhosis after curative therapy, highlighting the long-term sequelae that remain despite progress toward elimination (Abstract 441).

This progress may be threatened by ongoing sexual transmission of HCV. A Spanish cohort reported a plateau in the decline of acute HCV infections in people with HIV; risk for new HCV infection was significantly associated with chem-sex (incidence rate ratio [IRR], 4.9; $P=.03$) and previous sexually transmitted infections (IRR, 18.23; $P=.01$) (Abstract 445). Similarly, the German NoCo cohort (Cohort on HCV microelimination in MSM) reported no change in the incidence of new HCV infections an MSM cohort from 2014 to 2019, despite widely available HCV treatment (Abstract 442). Ongoing HCV transmission was attributed to delays in HCV treatment initiation and health insurance constraints. This German cohort also reported an incidence rate for HCV reinfection of 19/100 person-years in 222 MSM with previous HCV reinfection (Abstract 439). The majority (69%) had 1 reinfection, whereas the remaining 30% had 2 to 5 reinfections. Compared with MSM with a history of only 1 HCV infection, those reinfected were

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more likely to be older and to have HIV coinfection (odds ratio [OR], 5.5; P=.028), or use methamphetamine (OR, 6.6; P=.028) or ketamine (OR, 6.0; P=.07)

Given the high rates of incident HCV and reinfections in MSM with HIV, more frequent testing is needed in this population. Using a cost-effectiveness model for HIV and HCV transmission among MSM in the United Kingdom, a screening strategy of antibody testing every 6 months for MSM with HIV, annually for MSM on preexposure prophylaxis (PrEP), and at any time HIV screening was done for MSM not on PrEP was found to be cost effective at $35,000 per quality-adjusted life year (Abstract 440). In the model, testing at this threshold resulted in meeting a 90% incidence reduction goal among MSM in the United States by 2030 (paired with direct-acting antiretroviral [DAA] treatment of identified cases). Put in context, this supports a more aggressive testing strategy than currently recommended in MSM with HIV, which is at least yearly. A notable limitation in this preliminary cost-effectiveness analysis is that the cost of testing for reinfection, for which HCV RNA is required, was not considered.

To make progress on elimination goals, new testing strategies that are accessible and cost effective are needed. Modeling on the approach of self-testing for HIV and sexually transmitted infections (STIs), pilot studies were conducted using the OraSure® rapid saliva-based HCV antibody testing in several international locations among different populations at risk including MSM and people who inject drugs (PWID) (China, Vietnam, Georgia, and Kenya) as well as the general Egyptian population (Abstract 446). Although mistakes in the testing process were made frequently by participants, these mistakes did not appear to adversely impact test accuracy or result interpretation, with most sites showing more than 95% interobserver agreement and more than 90% concordance with results from a professional-use HCV antibody test. Additionally, many of these populations will have the need for repeated testing. In that setting, self-testing may provide substantial benefit.

Hepatitis C: Immunology and Inflammation

Female sex is associated with increased rates of spontaneous HCV clearance, although specific mechanisms associated with enhanced clearance are unknown. To gain further insight into immune response pathways that may be associated with HCV clearance, peripheral blood mononuclear cell (PBMC) gene expression was analyzed according to sex and HCV serostatus within the BBAASH (Baltimore Before and After Acute Study of Hepatitis) cohort (Abstract 461). In the HCV-seropositive group, PBMC collection occurred during acute infection (n=11), during chronic infection (n=24) and after clearance (n=4). A large number of genes were differentially expressed when comparing HCV-infected with –uninfected individuals. When considering differential gene expression between males and females, 151 genes were differentially expressed (as assessed by a false discovery rate [FDR] <0.05) between uninfected males and females. In the setting of HCV infection, that number increased to 2960 gene expression differences between males and females. Pathway analysis identified 24 custom pathways that were differentially activated in women with HCV infection. The authors highlighted mannose receptor, C type 1 (MRC1), which is part of the granulocyte-macrophage colony-stimulating factor (GM-CSF) differentiation pathway and is upregulated significantly more in women with HCV infection. Replication of the gene expression studies in larger cohorts combined with supporting mechanistic studies are needed to confirm these findings.

Mitochondrial function can impact immune response, and one method for codifying differences in mitochondrial DNA (mtDNA) is to determine ancestral mitochondrial haplogroups. In an exploratory analysis controlling for interferon-λ4 (IFNL4) genetic variants, mtDNA haplogroup frequency was compared between those with HCV clearance or persistent viremia in cohorts of European and African ancestry (Abstract 459). Clearance was significantly more frequent in those with mtDNA haplogroup I in the European ancestry cohort (OR, 2.0; P=.03). When stratified by HIV status, the association only remained significant in the HIV group (n=257; OR, 4.22; P=.05). Replication of the finding in other HIV/HCV cohorts is needed given the small numbers in the groups studied and relatively high P values for a genetic as sociation study.

Glycobiology is an emerging field and variable glycosylation patterns on proteins, such as immunoglobulin G (IgG), can impact protein-protein inter action and the inflammatory response.[1] HIV is associated with a proinflammatory state that is not completely reversed with antiretroviral therapy (ART). Altered glycosylation in the setting of HIV infection may contribute to this state, particularly through increased agalactosylated and hyposialylated IgGs that are associated with a proinflammatory state.[2] How HCV/HIV coinfection impacts the IgG glycomic signature is unknown. To explore this, a group of 249 African American participants in the ALIVE (AIDS Linked to the IntraVenous Experience) cohort was selected for determination of IgG glycosylation according to HCV and HIV status (Abstract 458). In the HIV groups, median CD4+ cell counts were 577/μL, and 469/μL, those with HIV but not HCV and those with HIV and HCV, respectively; however, relatively high percentages in both groups had detectable HIV RNA (22% and 33%, respectively). Consistently higher percentages of proinflammatory glycomic signatures were found within the plasma glycome of patients with active HCV infection; in particular, HCV/HIV coinfection was associated with the highest percentages of agalactosylated and hyposialyltaed glycans at levels significantly higher than all other groups.

Hepatitis C Treatment

DAAs have revolutionized HCV therapy; their 2 outstanding features are efficacy (>95% sustained virologic response [SVR]), independent of most

patient and disease characteristics, and excellent safety/tolerability. Building on these characteristics and the need to further simplify HCV treatment approaches to lower costs, particularly with availability of low-cost generic formulations of the therapies and to facilitate HCV elimination globally, final results of the AIDS Clinical Trial Group (ACTG) MINMON (Minimal Monitoring Study or A5360) have been eagerly awaited (Abstract 135). The MINMON approach consisted of confirmation of HCV viremia, routine laboratory evaluations to determine cirrhosis status (fibrosis-4 [FIB-4]), and exclusion of active hepatitis B virus (HBV) infection

In the MINMON study, sustained virologic response was attained in 95% (379/399) of participants, and no serious adverse events related to treatment occurred or resulted in discontinuation

(+HBsAg) followed by provision of a full 12-week course of sofosbuvir/velpatasvir (84 tablets) with no in-person follow-up or laboratory evaluations until SVR 12 weeks after completion of treatment (SVR12). Pretreatment HCV genotyping was not performed. Remote (telephone) contact was scheduled at weeks 4 and 22. The study enrolled 400 participants globally, including in Brazil (n=131), Thailand (n=110), Uganda (n=15) and South Africa (n=12) and 399 initiated study treatment. Participants were relatively young (median age, 47 years), 14% were black, 42% were HIV-coinfected, 9% had cirrhosis (FIB-4 ≥3.25), and 14% reported current substance use (ie, in the past 3 months). The international enrollment facilitated a broad HCV genotype representation including 20% with genotype 3 and 10% with genotypes 4 to 7. Sustained virologic response was attained in 95% (379/399) of participants, and no serious adverse events related to treatment occurred or resulted in discontinuation occurred.

Data from the Veteran's Administration (VA) system demonstrated high efficacy for DAA regimens regardless of alcohol use during treatment. Using the AUDIT-C (Alcohol Use Disorders Identification Test-Concise) score to gauge alcohol use, 77,045 courses of DAA therapy in VA system from January 2014 to December 2018 demonstrated an SVR of 94% irrespective of alcohol use, including 17% with high-risk AUDIT-3 scores of 4 or higher (adjusted odds ratio [aOR] for SVR in this group was 1.0 [95% confidence interval {CI}, 0.89-1.12]) (Abstract 459). The authors concluded that restrictions on DAA therapy based on ongoing alcohol use (or any other substance use for that matter) are not supported by the data and constitute unnecessary barriers that likely harm patients. However, independent of chronic viral hepatitis, excessive alcohol use remains a risk factor for liver disease. Among 11,891 Swiss HIV Cohort participants, all-cause mortality was associated with extremes of alcohol use with adjusted incidence rate ratios (aIRR) of 1.9 (95% CI, 1.5-2.3) and 1.8 (95% CI, 1.2-2.6) for abstinence and binge drinking, respectively (non-hazardous drinking on AUDIT-C as a reference) (Abstract 457). After adjustment for multiple confounders including body mass index (BMI), history of AIDS, and chronic viral hepatitis, only binge drinking was associated with an elevated aIRR of 4.0 (95% CI, 2.7-6.1) for liver-related events.

Data are slowly accumulating on DAA dosing in children with regimens now approved down to age 3 years and pangenotypic regimens to age 6 years. Daclatasvir is a pangenotypic nonstructural protein 5A (NS5A) inhibitor available a generic form in much of the world which, when paired with sofosbuvir, is a key component of an affordable pangenotypic DAA regimen. Using intensive pharmacokinetic (PK) data from 17 adolescents (ages 12-18 years) given 60 mg of daclatasvir once daily (standard adult dose) a population PK model was built and then used to simulate daclatasvir PK in adolescents 10 kg to 35 kg receiving either 30 mg or 60 mg once daily (Abstract 444). For children weighing 35 kg down to 14 kg, daclatasvir 30 mg modeling yielded maximum concentration (C_{max}) and area-under-the-concentration curve $(AUC)_{0-24}$ values comparable to those found in adults. In the 30 kg to 35 kg weight range, 60 mg daclatasvir also yielded PK parameters within range of adult dosing. Given what is also known about sofosbuvir dosing in children, standard doses of both sofosbuvir and daclatasvir could be used above 30 kg and 200 mg sofosbuvir with 30 mg daclatasvir used in those 17 to 30 kg.[3]

Before the introduction of DAAs, outcomes for liver transplantation in people with HIV who had HCV coinfection were poor and significantly worse than HIV-negative persons with HCV infection.[4,5] Excellent results have been obtained with DAA treatment of recurrent HCV posttransplant as well as in the setting decompensated liver disease before transplant, although data are needed in people with HIV. Results from the STOP-coinfection study utilizing sofosbuvir-based HCV treatment in people with HIV either 1) pretransplant in those with decompensated cirrhosis (Child's Pugh Turcotte [CPT] ≥7 and model for end-stage liver disease [MELD] 6-30) or 2) post-transplant with any stage of liver disease were reported (Abstract 467). Treatment was well tolerated and highly efficacious (93% SVR) with no compromise in HIV control. Although MELD scores improved in more than half the pretransplant cohort (53% with MELD <15, and 64% with MELD >15), the majority died or went on to require liver transplantation within the next 4 years. Conversely, those treated post-liver transplant had excellent survival similar to that seen in HIV-uninfected persons undergoing transplantation for HCV-related endstage liver disease (ESLD). The pretransplant data raise the question of whether there some threshold of decompensated cirrhosis beyond which it is preferable to forgo treatment and proceed to liver transplantation with HCV treatment as soon as possible after transplant.

Drug-use stigma can impact HCV and HIV acquisition by inducing riskier behaviors in individuals seeking to avoid stigmatizing interactions or creating decreased sense of self-worth. To quantify stigma in 4 specific domains (vicarious, enacted, felt normative, and internalized stigma) an electronic survey was administered to 11,663 PWID across 12 sites in India (Abstract 447). Stigma levels were then compared with HCV prevalence. The population was mostly young (average age 30 years) and male (94%) with 73% injecting in the last 6 months and 34% with active HCV infection. The OR for active HCV infection was significantly higher in groups that had experienced enacted stigma (overt acts directed at an individual because of their drug use) (OR, 1.35) and that scored in the top 75th percentile for internalized stigma (self-stigma) (OR, 1.52-1.84). Further, enacted stigma correlated with significantly increased reporting of high-risk behaviors such as sharing of needles or syringes and multiple injection partners. Although it is clear that strategies to remove or decrease injection drug-use stigma are needed, effective approaches remain elusive.

Modeling studies demonstrate that combined modalities are necessary to effectively treat and eliminate HCV in PWID, particularly in settings with moderate to high HCV prevalence. Medications for opioid-use disorder (MOUD) and syringe service programs (SSPs) are essential components in addition to DAA scale up. An analysis from the Canadian coinfection cohort assessed trends in HCV treatment and supportive services usage over time among PWID, HIV (n=1090) who had injected drugs during different time periods (2003-2010, 2011-2013, and 2014-2019) (Abstract 448). A large increase in treatment and effectiveness was seen in 2014 due to the introduction of DAAs. However, no comparison was made to rates in HCV/HIV-coinfected persons who did not inject drugs to investigate if there was still hesitancy to treat in the PWID group. Access to SSPs was generally high (>80% reported access during visits) in the first 2 time periods, but a concerning drop was reported for 2014 to 2019 (~60% access). MOUD access was low across all time periods (~20% reporting access). Encouragingly, reported needle/syringe sharing was low and significantly decreased over time. In the DAA era initiations at 20/100 person-years are generally above modeling thresholds identified for elimination when combined with harm reduction services. Despite this, there is clearly room to increase treatment uptake and make harm reduction services more available for HCV/HIV PWID in Canada (and elsewhere).

Hepatitis B

Two of the symposia that focused on the liver addressed novel approaches to HBV control and cure: new prospects for treatment of HBV and harnessing immunity to cure HBV.

HBV Treatment: Consequences of Persistent Viremia

Most data assessing the risk for hepatocellular carcinoma (HCC) in chronic HBV infection come from HBV-monoinfected populations. The NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) cohort assessed the risk for HCC in more than 8000 HIV/HBV-coinfected individuals. The incidence rate was 1.8/1000 person-years (95% CI, 1.5-2.1) during a median follow-up of 6.9 years. HCC incidence was significantly associated with age older than 40 years (adjusted hazard ratio [aHR], 2.14), HCV antibody positivity (aHR, 1.6), heavy alcohol use (aHR, 1.51), but not with race, HIV viral load, or CD4+ cell percentage. HBV viral load was correlated with HCC risk in a dose-dependent manner, that is an aHR of 1.18 for each 1.0-$\log_{10}$ IU/mL increase, and with HBV DNA level above 200 IU/mL (aHR, 2.7), which is well below the HBV viral load threshold for HBV treatment initiation in most guidelines. Undetectable HBV for more than a year was also associated with lower HCC rate, compared with detectable HBV or undetectable for less than a year. These data suggest that in HIV/HBV-coinfected patients, sustained suppression of HBV replication may be key to reducing HCC risk, rather than simply getting HBV below a certain threshold, as well as addressing other drivers of hepatic inflammation such as heavy alcohol use and HCV infection (Abstract 136). Attaining HBV virologic suppression can take a long time, particularly in HIV/HBV-coinfected individuals. Of 222 starting tenofovir-based treatment in the Swiss HIV cohort, 84% had detectable HBV DNA and 58% had HBV level above 2000 IU/mL. HBV viremia persisted in 27% at 2 years and in 18% at their latest follow-up; HBV DNA level was above 2000 IU/mL in 10% and 13% of these viremic patients, respectively. Persistent viremia was associated with high baseline HBV DNA level (OR, 1.24; 95% CI, 1.07-1.44) and advanced HIV (Centers for Disease Control and Prevention [CDC] Stage 3) (OR, 2.8; 95% CI, 1.18-6.6), but was not associated with hepatitis delta (HDV) coinfection. No HBV resistance testing was performed; however, HBV resistance to tenofovir is rare (Abstract 450).

HBV undetectable for more than a year was associated with lower HCC rate, compared with detectable HBV or undetectable for less than a year

HBsAg loss represents a "functional cure" of HBV with immunologic control and is uncommon; typically in 1% per year in HBV-monoinfected patients, even with effective HBV treatment with HBV DNA suppression.[6] In the Swiss HIV cohort, of 272 HIV/HBV-coinfected patients, HBsAg loss occurred in 8% during the first 2 years of tenofovir therapy and 16% after a median of 8.4 years of follow-up, which is higher than generally seen in HBV monoinfection. When HBsAg clearance occurred, more than half (54%) developed anti-HBs antibodies, suggesting durable immunologic control. HBsAg clearance was associated with female sex (OR, 9.15;

95% CI, 1.08-77) and low baseline quantitative HBsAg at baseline (OR, 12.01; 95% CI, 2.5-57.7). The reason for higher HBsAg loss in HIV/HBV coinfection is an area of active investigation (Abstract 449).

Hepatitis Delta

HDV is an important driver of hepatic morbidity and mortality in chronic hepatitis B; however, coinfection rates vary widely by region and risk factor. In the Swiss HIV cohort and EuroSIDA cohorts, HDV Ab prevalence in more than 2700 HIV/HBV-coinfected individuals was 15.2%, 66% of whom had active HDV viremia. HDV antibody positivity was twice as high in Eastern Europe (32.8%) and Southern Europe (29.7%) than in Northwestern Europe (15%). PWID comprised half of all HDV infections. HDV infection was associated with significantly higher mortality (aHR, 1.4), liver-related death (aHR, 2.9), and HCC (aHR, 6.5) than in those without HDV (Abstract 452). In a Taiwanese cohort of 505 HIV/HBV-coinfected patients, HDV Ab baseline prevalence was lower at 6.5%. However, an additional 8.1% seroconverted while on tenofovir-containing ART over a 7-year time period, with an incidence rate of 16.5 per 1000 person-years of follow-up. Of these newly HDV-infected patients, all were male, 88% were MSM, 5% were PWID, and 77% had undetectable HBV viremia. These data are a reminder to screen HIV/HBV-coinfected persons for HDV, particularly those from regions with high HDV prevalence; populations at risk may vary substantially by region.

HBV Vaccination

HBV vaccination is the cornerstone of HBV prevention; however, efficacy can be impaired by HIV infection as well as vaccine escape mutations. In a cohort of perinatally infected people with HIV matched with those infected in adulthood, reactive HBsAb was present in 35% of those with perinatal HIV and 64% in those infected as adults (aOR, 0.4; 95% CI, 0.2-0.82), despite receipt of more HBV vaccinations in the perinatally infected group. The overall suboptimal seroprotection rate of 50% is reminder to prioritize vaccination in people with HIV and to confirm HBsAb after vaccination particularly in those who are perinatally infected as additional vaccination may be necessary (Abstract 451). HBsAg "vaccine escape" mutations can reduce HBV vaccine efficacy and thwart HBV diagnosis, by leading to HBsAg negativity despite ongoing viremia. In an Italian evaluation of more than 900 patients viremic with HBV genotype D (common in Mediterranean, Northern African, and Asian regions), 21 different vaccine escape mutations were identified. A total of 17.8% had at least 1 mutation, and 3% had 2 or more mutations. Having more mutations was associated with a higher likelihood of HBsAg negativity despite HBV viremia; 35% of those with 2 or more mutations were HBsAg negative and viremic. There was a significant increase in prevalence of patients with mutations over time, from 0.4% in 2005 to 2009 to 5.1% in 2015 to 2019 ($P = .007$) (Abstract 137).

Hepatitis A

Recent outbreaks of hepatitis A in MSM and people with HIV are a reminder of inadequate vaccination for this preventable viral disease. In a cohort of more than 3000 people with HIV in Texas, less than 10% of patients eligible for hepatitis A virus (HAV) vaccination had been vaccinated after 2 years in care. Latinx people with HIV were less like to receive a full HAV vaccine series (hazard ratio [HR], 0.51), whereas MSM and those with HBV or HCV infection were more likely receive HAV vaccination (Abstract 464). A Spanish cohort of 272 HAV-susceptible people with HIV also reported low HAV vaccine uptake, with 38% undergoing vaccination over a 10-year period. Nearly 10% of those vaccinated did not show HAV seroconversion, and 1 individual lost HAV antibodies. Several HAV outbreaks occurred during follow-up, the majority of infections (60%) occurring in nonimmunized MSM (Abstract 466). To examine optimal strategies for HAV revaccination in those with ineffective initial vaccination, a Taiwanese study randomly assigned 102 men with HIV to 1 or 2 HAV vaccines after initial nonresponse or seroreversion. There was no significant difference in seroconversion with 1 dose (79%) versus 2 doses of HAV vaccination (84%); those with prior seroreversion had a 100% response to either 1 or 2 doses. Of note, 2 doses led to a 2-fold higher HAV antibody level at week 24; however, whether this will translate to longer lasting protection in this population is not known (Abstract 465).

Fatty Liver Disease

Fatty liver disease has been an increasing driver of hepatic-related morbidity and mortality in people with HIV. There was an excellent overview of mechanisms and treatments of steatosis in HIV in the "Focus on the Liver" (Symposium 11).

Given the rising importance of fatty liver disease, more accurate diagnostic tools are needed, particularly for nonalcoholic steatohepatitis (NASH) where the standard remains liver biopsy. In a cohort of 69 people with HIV with persistent transaminase elevations and accompanying liver biopsies accuracy of imaging, biomarker assays (triglyceride glucose index [TyG], fatty liver index [FLI], and hepatic steatosis index [HSI]) and combinations were evaluated (Abstract 460). Ultrasound and controlled attenuation parameter (CAP) alone performed better than biomarker assays (area under the receiver operating characteristic curve [AUROCs] of 0.90 or higher with high sensitivity and positive predictive value [PPV]) (Abstract 460). Although combining markers with CAP improved AUROC negative predictive value in particular, the main issue is not diagnosis of steatosis but determination of nonalcoholic steatohepatitis (NASH) and associated fibrosis, as this group is where intervention is indicated. Combining transient elastography (TE)/CAP with aspartate aminotransferase (AST) level to determine the FibroScan-AST (FAST) score may assist in this determination. In a German cohort of people with HIV, 319 individuals had at least 2 FAST assessments from 2013 to 2018 (Abstract 455). There were significant increases in FAST and CAP scores with

serial measurement over time within the cohort. Although significantly positive correlations between baseline FAST and CAP score, FIB-4, and AST-to-platelet ratio index were found, this is not surprising because all share common components or measurements. Univariate associations with factors (BMI, diabetes, hyperlipidemia, and integrase strand transfer inhibitor [InSTI]) known to predispose to weight gain or NASH and higher FAST scores were found. Although it is likely that FAST will be a useful screening tool for NASH in people with HIV and the reported associations are encouraging, further validation is needed, in particular with liver biopsy.

ESLD in HIV: Etiology and Management

Complications of ESLD remain a major source of mortality for people with HIV and prediction models for future decompensation in persons with underlying liver disease are lacking. Using the NA-ACCORD cohort, participants with a FIB-4 score above 1.45 and in care from 2000 to 2016 were examined for outcomes of decompensated liver disease to derive a predictive model (Abstract 468). Among the 13,787 eligible participants, chronic viral hepatitis (HBV or HCV) were the strongest predictors; excluding those infections, Bayesian modeling selected 10 other predictors of future decompensation that included demographics (age, sex, and race), as well as markers of hepatic inflammation (eg, AST level), serum albumin (ALB), portal hypertension, total bilirubin, platelets, and lipid levels. The AUROC in the derivation cohort for this set of 10 factors was 0.78 and was validated in a test cohort (AUROC, 0.8). Further, a dramatic increase in the rate of ESLD events was found for those in the highest 2 deciles for the risk score. Notably, no HIV disease characteristics made it into the final model. Although this a welcome step toward defining predictive models for hepatic decompensation in people with HIV, the predominant effect of chronic viral hepatitis and alcohol use on decompensation events limits the value of the additional model factors.

Endoscopic screening for esophageal varices may be omitted for patients with cirrhosis who meet certain liver stiffness and platelet count thresholds.[7] However, these thresholds were derived based on determinations made in persons with active liver disease, including untreated HCV. How well these criteria perform after cure of HCV, particularly in people with HIV, is not understood. Using the GEHEP (Group for the Study of Viral Hepatitis) cohort (n = 428), performance of various criteria (HEPAVIR [Estudio de las Hepatitis Viricas]: liver stiffness, <21 kPa; Baveno VI: liver stiffness, <25 kPa, and platelet count >110/µL, and HIV cirrhosis: liver stiffness, <30 kPa and platelet count >110/µL) was assessed based on updated measurements at the time of SVR (Abstract 469). All criteria performed extremely well with a negative predictive value (NPV) for variceal bleed of more than 99.5% and avoiding unnecessary endoscopies in 40% to 45% of patients. The performance was identical to that in the HIV coinfection cohort (n=257). An open question remains whether even higher liver stiffness and lower platelet count thresholds would perform equally well and avoid additional upper endoscopies.

Effects of ART on the Liver

Modern ART regimens are potent, well tolerated, and generally safe, but adverse impacts of antiretroviral drugs (ARVs) may be difficult to detect in trials with relatively small numbers of patients followed up for short durations. Data from NA-ACCORD used a Bayesian Cox model to assess for signals indicating potential contributions to liver-related events by comparing prior and posterior credible intervals (CrI) for events according to different ARVs or covariates such as viral hepatitis or alcohol use (Abstract 456). As expected, clear signals were present for adverse impacts of HCV or HBV infection on liver outcomes (HR for HCV, 4.4; 95% CrI, 2.6-7.0). In contrast, modest, and potentially detrimental effects, were noted for the HIV protease inhibitors atanazanvir (HR, 1.8; 95% CrI, 0.82-3.9) and darunavir (HR, 2.0; 95% CrI, 0.86-4.7). Neutral effects were suggested for the nucleos(t)ide reverse transcriptase inhibitors (nRTIs) abacavir and tenofovir. Although of interest, the data are not definitive and should be viewed as hypothesis generating. Given the weight gain associated with InSTIs, it would be interesting to know if there was a signal with these ARVs and adverse liver outcomes. Unfortunately, data for a sufficient period of time were not available to judge their potential impact. The field must remain vigilant to possible toxic (or beneficial) effects of ARVs on liver disease progression; a major take away remains the profound impact of viral hepatitis coinfection as well as alcohol use and the need to ensure patients are evaluated and treated for these comorbidities.

SARS-CoV-2 and the Liver

Transaminitis is frequently detected during COVID-19 infection though clinically significant hepatic injury is extremely rare. In vitro experiments were conducted in 2 liver cell lines, Huh-7.5 and HepG2 with a fixed amount (multiplicities of infection [MOI] of 0.1) of SARS-CoV-2 (Abstract 462). Robust SARS-CoV-2 production in supernatants was observed; although at levels 1- to 2-$\log_{10}$ lower than Vero-E8 or WI-38 cells (a lung cell line). Cytopathic effects were seen as early as day 3 postinfection in Huh-7.5 cells. The results demonstrate that, despite a paucity of angiotensin-converting enzyme 2 (ACE2) expression, liver cells lines are capable of being infected by SARS-CoV-2 with resulting cell death. Attempts to replicate these findings in primary human hepatocytes would be informative. The results suggest at least 1 pathophys-

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iologic mechanism by which transaminase elevations may occur with COVID-19.

All cited abstracts appear in the CROI 2021 Abstract eBook, available online at www.CROIconference.org

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