Review

CROI 2015: Highlights of Viral Hepatitis Therapy

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High cure rates with all-oral regimens for patients with HIV/hepatitis C virus (HCV) coinfection were a highlight of the 2015 Conference on Retroviruses and Opportunistic Infections. Twelve weeks of sofosbuvir and daclatasvir led to sustained virologic response (SVR) rates of 96% in treatment-nave and 98% in treatment-experienced HCV genotype 1–infected patients. Twelve weeks of sofosbuvir plus ledipasvir had similar results, with SVR rates of 95% in treatment-naive and 96% in treatment-experienced patients. Patients with cirrhosis were included in both trials and attained SVR rates of 92% to 94%. Real-world performance of sofosbuvir and simeprevir resulted in SVR rates similar to those attained in clinical trials. Identifying HCV infection, linking patients to care, reducing barriers to drug access, and ensuring adherence will be key to realizing the enormous potential of high cure rates with interferon alfa–free therapies. Preventing reinfection after cure will be of particular importance in the HIV-infected population, which was highly impacted by reinfection rates of more than 20% during 5 years of follow-up in a meta-analysis.

Keywords: CROI 2015, hepatitis, HIV, HIV/HCV coinfection, direct-acting antivirals, DAAs, hepatitis C virus, HCV, sofosbuvir, ledipasvir, daclatasvir

Clinical Trials of Direct-Acting Antiviral Regimens in HIV/HCV Coinfection

Among the most anticipated hepatitis C virus (HCV) data from the 2015 Conference on Retroviruses and Opportunistic Infections (CROI), held from February 22 to 26, were 2 late-breaking presentations that delivered the first sustained virologic response (SVR) with undetectable HCV RNA 12 weeks after therapy completion (SVR12) results from phase III studies of interferon alfa–free direct-acting antiviral (DAA) treatments in HIV/HCV-coinfected patients (Table 1). The ALLY-2 study evaluated sofosbuvir (a nonstructural protein [NS]5B polymerase inhibitor) and daclatasvir (an investigational NS5A antagonist) (Abstract 151LB), and the ION-4 study evaluated the fixed-dose combination of sofosbuvir plus ledipasvir (an NS5A antagonist) (Abstract 152LB). Both studies examined sofosbuvir plus an NS5A antagonist, evaluated 12 weeks of therapy in treatment-naive and -experienced patients (including those with cirrhosis), and omitted ribavirin from the regimen. Despite these similarities, there were a number of key differences. Given the broad genotypic coverage of daclatasvir, patients with HCV genotypes 1 to 6 were eligible for the ALLY-2 study (although only genotypes 1-4 were enrolled). Owing to predictable drug interactions and the ability to dose adjust daclatasvir, nearly all antiretroviral regimens were allowed in the study, including ritonavir-boosted (/r) HIV protease inhibitor (PI)-based regimens. Finally, ALLY-2 was the first trial to evaluate a shortened (8-week) therapeutic course for HCV treatment–naive, HIV/HCV-coinfected patients. The ION-4 study was more straightforward in design, evaluating a single fixed-dose combination in all patients for 12 weeks, and thus enrolled a larger number of patients and more patients with cirrhosis than did ALLY-2. Antiretroviral regimens were limited to tenofovir and emtricitabine in combination with either raltegravir, rilpivirine or efavirenz. Perhaps most importantly, sofosbuvir and ledipasvir are currently available to HIV/HCV-coinfected patients in the United States, but daclatasvir is not yet approved by the US Food and Drug Administration, although both regimens are approved for use in Europe.

Sofosbuvir and Daclatasvir

The ALLY-2 study enrolled 203 patients, including 101 treatment-naive patients who were treated for 12 weeks, 50 treatment-nave patients who were treated for 8 weeks, and 52 treatment-experienced patients who were treated for 12 weeks. The daclatasvir dose was adjusted to 90 mg for those taking efavirenz or nevirapine, to 30 mg for those taking a PI/r, and was kept at the standard 60 mg daily for all others. The majority of patients were men infected with HCV genotype 1a, 34% of patients were black, and 29% of treatment-experienced patients had cirrhosis.

The vast majority of patients had well-controlled HIV infection, with a median CD4+ count of greater than 500 cells/μL. The most common antiretroviral regimens included 2 nucleoside analogue reverse transcriptase inhibitors plus one of the following: raltegravir, efavirenz, atazanavir/r, or darunavir/r. Overall, treatment was safe and well tolerated, with good maintenance of HIV control. SVR12 rates for all patients with HCV genotype

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Table 1. Selected Phase III Clinical Trial Results for Patients Coinfected With HIV and HCV Genotype 1[a]

CROI 2015 Abstract (Study)	Regimen	No.	SVR12 Rate	Treatment Naive	Treatment Experienced	No Cirrhosis	Cirrhosis
151LB (ALLY-2)	Sofosbuvir and daclatasvir[b] for 12 weeks	127	97%	96% (80/83)	98% (43/44)	98%[c] (98/100)	91%[c] (20/22)
151LB (ALLY-2)	Sofosbuvir and daclatasvir[b] for 8 weeks	41	76%	76%	NA	78% (28/36)	60% (3/5)
152LB (ION-4)	Sofosbuvir and ledipasvir for 12 weeks	327	96%	95% (138/146)	97% (175/181)	96% (250/260)	94% (63/67)

Abbreviations: CROI, Conference on Retroviruses and Opportunistic Infections; HCV, hepatitis C virus; NA, not applicable; SVR12, sustained virologic response 12 weeks after cessation of therapy.

[a]See text for additional details. Subgroups calculated from data presented.

[b]Investigational drug in the United States.

[c]5 participants had indeterminate cirrhosis status at baseline; all achieved SVR12.

1 treated for 12 weeks were 96% for treatment-naive patients and 98% for treatment-experienced patients; response rates for all HCV genotypes were similar at 97% and 98%, respectively. Given these high SVR12 rates, no baseline factors clearly impacted response to 12 weeks of therapy, although relatively few patients with cirrhosis were present in each study arm (9 in the treatment-naive arm and 15 in the treatment-experienced arm).

Response rates with 12 weeks of therapy were 100% for genotype 2 and 100% for genotype 3. However, given the limited number of patients in the 12-week study arms, little can be said with certainty regarding the efficacy of treatment in these HIV/HCV-coinfected patients. Results from dedicated studies such as ALLY-3 are more reliable for predicting treatment response in individuals with HCV genotype 3 infection and still suggest limitations of 12 weeks of sofosbuvir and daclatasvir for treatment-experienced individuals with genotype 3 (SVR12 rate, 86%) and for those with genotype 3 and cirrhosis (SVR12 rate, 63%).[1]

In ALLY-2, the SVR12 rate was 76% with 8 weeks of treatment, substantially lower than the SVR12 rate of 97% to 98% seen with 12 weeks of treatment, and did not differ based on HCV genotype. This was surprising, given the high SVR rate (94%) attained in HCV-monoinfected patients with 8 weeks of a similar regimen of sofosbuvir plus ledipasvir.[2] Although ALLY-2 was not powered to detect differences in SVR by baseline factors after 8 weeks of treatment, patients taking darunavir/r were overrepresented in the 8-week arm and did have a numerically lower response rate (67%). Of note, drug-drug interaction data presented after the trial began indicate that darunavir/r does not increase levels of daclatasvir exposure to the same extent that atazanavir/r does.[3] As a result, current dosing guidelines recommend using 60 mg of daclatasvir for patients taking darunavir/r or lopinavir/r.

Sofosbuvir Plus Ledipasvir

The ION-4 study enrolled 335 patients in a single 12-week treatment arm of sofosbuvir plus ledipasvir. The majority of the patients were men (82%) with HCV genotype 1 infection (98%; patients with genotype 4 were also enrolled) and 34% were black. Slightly more than half of patients were treatment experienced (55%) and 20% had cirrhosis. Ninety-two percent of patients were taking raltegravir or rilpivirine, each with tenofovir and emtricitabine. HIV infection was well controlled, with a median CD4+ count of 628 cells/μL. Overall SVR12 rate was 96% (95% in treatment-naive patients and 97% in treatment-experienced patients). The presence of cirrhosis did not impact response rates. Curiously, all 10 patients who experienced viral relapse were black, including 8 who were taking efavirenz. This association of black race and viral relapse was statistically significant in a multivariate analysis, although no difference in sofosbuvir or ledipasvir exposure was found based on a population pharmacokinetic analysis. The explanation for the lower response rates remains unclear at this time.

Data were presented for the pharmacokinetic interactions of sofosbuvir plus ledipasvir and darunavir/r, atazanavir/r, or tenofovir in healthy volunteers (Abstract 82). The effect of antiretroviral drugs on sofosbuvir, sofosbuvir metabolite (GS-331007), and ledipasvir concentrations was not judged to be clinically significant.

However, sofosbuvir plus ledipasvir coadministered with darunavir/r raised tenofovir trough concentrations at end of dosing interval by 59% and area under the curve by 50%, and coadministration with atazanavir/r raised tenofovir trough concentrations by 47%. The mechanism was postulated to be persistent inhibition of efflux drug transporters. Ritonavir-boosted HIV PIs raise plasma tenofovir levels in the absence of sofosbuvir plus ledipasvir, thus this represents a further increase of tenofovir concentrations with the addition of sofosbuvir plus ledipasvir. The clinical impact of these elevated concentrations during 12 weeks of HCV therapy are unknown. Current prescribing information recommends avoiding coadministration of a PI/r and tenofovir with sofosbuvir plus ledipasvir, if feasible, or close monitoring of renal function if coadministration is necessary.

These data from the ALLY-2 and ION-4 trials represent the first phase III SVR data on contemporary DAA regimens for individuals with HIV/HCV coinfection. These data reinforce the notion that HIV/HCV-coinfected patients respond similarly to DAA

therapy as do HCV-monoinfected patients (with 12 weeks of therapy) and that sofosbuvir plus an NS5A antagonist is a remarkably potent and well-tolerated treatment option for this population. Drug interactions remain a limitation of therapy with sofosbuvir plus ledipasvir; however, the degree to which increased tenofovir concentrations during coadministration with sofosbuvir and ledipasvir will be seen in HIV/HCV-coinfected patients and, more importantly, whether this will be clinically significant remains unanswered. Clinical trial data for HIV/HCV-coinfected patients that address this potential interaction are eagerly awaited.

Hematologic Events With Paritaprevir/r, Ombitasvir, and Dasabuvir

The TURQUOISE-1 trial evaluated a regimen of paritaprevir/r (an HCV PI), ombitasvir (an NS5A inhibitor), and dasabuvir (a nonnucleoside NS5B polymerase inhibitor) given with weight-based ribavirin to HIV/HCV-coinfected patients for 12 weeks or 24 weeks.[4] In an analysis of grade 1 or 2 hematologic events, hemoglobin level declines occurred in 58% (18/31) of patients during 12 weeks of treatment and in 65% (21/32) of patients during 24 weeks of treatment, requiring ribavirin dose reductions for 4 and 2 patients, respectively (Abstract 691). All patients whose ribavirin doses were reduced attained an SVR.

Clinical Trials of DAA Regimens for HCV-Monoinfected Patients

Daclatasvir, Beclabuvir, and Asunaprevir

The UNITY-1 and UNITY-2 trials provided more data on the performance of a regimen of daclatasvir (an NS5A inhibitor), beclabuvir (an investigational nonnucleoside NS5B inhibitor), and asunaprevir (an investigational HCV PI). In the phase III UNITY-1 study, 12 weeks of this regimen given without ribavirin led to an SVR12 in 92% of HCV treatment-naive and 89% of treatment-experienced HCV-monoinfected patients with genotype 1 who did not have cirrhosis (Abstract 687). Comparing responses by HCV genotype, SVR12 rates were 8% higher in treatment-naive patients with genotype 1b than in those with genotype 1a, and 15% higher in treatment-experienced patients with genotype 1b than in those with genotype 1a. All confirmed virologic relapses were in patients with HCV genotype 1a. Baseline NS5A resistance did not negatively impact SVR in patients with HCV genotype 1b (100% [17/17] attained an SVR), whereas baseline resistance may have affected patients with HCV genotype 1a (74% [25/34] attained an SVR). Of the 25 patients who experienced virologic failure and had resistance test results available, 10 had resistance to all 3 drug classes and 14 had resistance to only NS5A or NS3.

Ribavirin may still be necessary for some subgroups treated with the investigational drugs daclatasvir, beclabuvir, and asunaprevir.

The UNITY-2 study examined the same 12-week regimen of daclatasvir, beclabuvir, and asunaprevir given with or without weight-based ribavirin to HCV genotype 1–monoinfected patients with cirrhosis (Abstract 688). In patients with HCV genotype 1a, the addition of ribavirin was associated with nonstatistically significant increases in SVR rates from 90% to 97% in treatment-naive patients and from 86% to 91% in treatment-experienced patients. Treatment-naive patients with HCV genotype 1b had a 100% SVR rate with or without ribavirin, and treatment-experienced patients with genotype 1b had SVR rates of 90% without ribavirin and 100% with ribavirin. Thus, in the presence of cirrhosis, there appears to be some benefit to the addition of ribavirin to patients with HCV genotype 1a and treatment-experienced patients with genotype 1b. It is unknown if ribavirin would improve SVR rates in HCV genotype 1a–infected patients without cirrhosis. As with the UNITY-1 study, baseline NS5A resistance did not appear to impact SVR. Of 13 treatment failures with resistance data available, 3 had resistance to all 3 drug classes and 8 had resistance to 1 or 2 drug classes. This regimen was generally well tolerated; as expected, the addition of ribavirin increased adverse effects, including anemia, fatigue, pruritus, and insomnia.

Collectively, these data demonstrate an overall high rate of SVR with the 12-week regimen of daclatasvir, beclabuvir, and asunaprevir and highlight that SVR rates are slightly decreased in patients with HCV genotype 1a and in those with prior treatment experience. Ribavirin may still be necessary for subgroups treated with this regimen, including patients with HCV genotype 1a and cirrhosis and treatment-experienced patients with genotype 1b and cirrhosis. Although virologic failures are uncommon, resistance to more than 1 drug class is common, and optimal retreatment strategies for these patients are needed.

Real-World Performance of DAA Regimens

Several studies examined response rates to DAA-based therapy outside the highly controlled settings of clinical trials. A German cohort examined outcomes of patients infected with HCV genotype 1 or 4 who were treated with sofosbuvir-based therapy. Of the 130 patients with SVR12 results available, approximately one-third were HIV infected. The 108 patients treated with sofosbuvir, peginterferon alfa, and ribavirin had an SVR12 rate of 85%, similar to the 90% response rate seen in a clinical trial.[4] The SVR12 rate for 15 patients treated with sofosbuvir and simeprevir was 87%, also similar to published clinical trial results.[5] HIV coinfection was not associated with decreased SVR rates; however, cirrhosis was associated with a 10% decrease in SVR12 rates ($P > .05$) (Abstract 646).

In another abstract that reported on real-world outcomes with sofosbuvir and simeprevir in 81 HCV genotype 1–infected patients, SVR12 rate was 77%

Table 2. Real-World Performance of Sofosbuvir and Simeprevir in HIV/HCV-Coinfected Patients by Pretreatment Fibrosis Stage and HCV Genotype[a]

	Cohort			SVR12			
CROI 2015 Abstract (Authors)	No.	Treatment Experienced	Metavir Fibrosis Stage F3 or F4	Genotype 1	Genotype 1a	Genotype 1b	Comments
644 (Marks et al)	15	100%	67% (F4 only)	93% (14/15)	--	--	All prior HCV PI treatment failures without detectable resistance
645 (Gilmore et al)	37	49%	78%	81% (30/37)	74% (17/23)	93% (13/14)	ITT analysis; 4/7 treatment failures were lost to follow-up (all 4 attained SVR4)
647 (Del Bello et al)	34	53%	56%	90% (26/29)	--	--	As treated
649 (Grant et al)	33	--	53% (F4 only)	95% (18/19)	92% (11/12)	100% (7/7)	As treated; 1 patient treated for 24 weeks

Abbreviations: CROI, Conference on Retroviruses and Opportunistic Infections; HCV, hepatitis C virus; ITT, intention to treat; PI, protease inhibitor; SVR4(12), sustained virologic response 4 (12) weeks after cessation of therapy.

[a]All patients treated for 12 weeks unless noted. Ribavirin used in some patients; unable to assess impact of ribavirin in these datasets.

in HIV/HCV-coinfected patients and 71% in HCV-monoinfected patients, and remained high (77%-78%) in the presence of cirrhosis. Half of the patients who did not attain an SVR12 were lost to follow-up and did not reflect confirmed virologic failures (Abstract 645). In several smaller cohorts of HIV/HCV-coinfected patients, many of whom were treatment experienced, treatment with sofosbuvir and simeprevir resulted in SVR12 rates of 93% to 95% (Abstracts 644 and 649) (Table 2). Of note, ribavirin was used in addition to simeprevir and sofosbuvir for some participants; however, studies were not powered to evaluate a difference in efficacy with and without ribavirin. These responses are similar to the SVR12 rates of 92% to 94% reported in the COSMOS (Combination of Simeprevir and Sofosbuvir in HCV Genotype 1–Infected Patients) trial.[6] Sofosbuvir-based HCV treatment was generally well tolerated, with the expected adverse effect of anemia when ribavirin was added to the regimen.

These studies continue to demonstrate that SVR12 rates with new oral HCV regimens outside of clinical trials are high and often approach those attained in clinical trials. Unlike what was seen in the interferon alfa era, current DAA regimens when used for HIV/HCV coinfection have generally not been associated with decreased cure rates or increased adverse events compared with HCV monoinfection. Loss to follow-up was an important contributor to failure to achieve an SVR. Thus, although current DAA regimens are much better tolerated than interferon alfa–containing regimens, there is a continued need for adherence support and posttreatment follow-up to ensure treatment completion and documentation of response.

Cost of DAA-Based Regimens

The high cost of HCV DAAs remains a central theme in discussions of new therapies and limits widespread use in those with HCV infection. Despite this high cost, new DAA regimens for HCV genotype 1 have generally been shown to be cost-effective when judged by the standard metric of an incremental cost-effectiveness ratio of approximately US $50,000 per quality-adjusted life-year.[7] Given the much-improved efficacy and tolerability profile of new DAAs, another key concept is analysis of the cost per cure when considering the total cost of treating persons with HCV infection.

Bichoupan and colleagues analyzed the cost per SVR of peginterferon alfa and ribavirin with telaprevir. In these initial studies, the cost per SVR was calculated to be approximately US $190,000.[8] In an updated analysis, Bichoupan presented data on 202 consecutive patients treated with sofosbuvir and simeprevir with or without ribavirin (173 patients had outcome data available) (Abstract 149). The patients treated in this series generally had a difficult-to-treat phenotype, were treatment experienced (70%, including 24% whose treatment with telaprevir or boceprevir had failed), and more than half had advanced fibrosis defined as a Fibrosis-4 (FIB-4) score of greater than 3.25. SVR rate for the cohort was 88% and mirrored that seen in clinical trials. The addition of ribavirin did not appear to impact SVR rate, although those who received ribavirin were enriched for prior failure and receipt of a PI.

In a multivariate analysis, prior telaprevir- and boceprevir-based treatment failure was associated with a sta-tistically significantly lower likelihood of achieving an SVR (odds ratio, 0.24; 95% confidence interval [0.09-0.63]; 76% SVR12 rate), perhaps

suggesting an impact of prior PI treatment failure and resistance to subsequent treatment with a cross-resistant component (simeprevir). Prior telaprevir- or boceprevir-based therapy has not been noted in studies to impact treatment with sofosbuvir plus an NS5A inhibitor or with paritaprevir/r, ombitasvir, and dasabuvir.[9,10] The cost per SVR was US $171,145, with drug costs making up 98% of this total. Still, this is lower than the cost per SVR seen with telaprevir-based therapy, reflecting the improved efficacy and tolerability of interferon alfa–free DAA regimens. Given the almost complete dependence of cost per SVR on drug costs, it is not surprising that in sensitivity analyses as the cost of drugs decreases so does the cost of SVR. With a 50% drug price discount (from wholesale prices) the cost per SVR was US $86,547.

Predictors of Adherence to DAA Regimens

Given the cost and increasingly shorter durations of DAA regimens, identifying predictors and barriers to adherence is key to treatment success with widespread implementation of DAAs in clinical practice. In an analysis of 2 clinical trials (SYNERGY and ERADICATE) evaluating treatment with ledipasvir plus sofosbuvir, adherence rate exceeded 90% and did not differ between HCV-monoinfected and HIV/HCV-coinfected participants, whether or not the latter were taking antiretroviral therapy (Abstract 692). Of note, there was a substantial decline in adherence over 12 weeks of therapy in all groups, emphasizing the need for adherence support and shorter regimens to optimize the success of DAA treatments. In 3 studies (SPARE, SYNERGY, and ERADICATE) evaluating sofosbuvir-based treatment, the presence of mental health disorders did not have a substantial negative impact on adherence or SVR rate (Abstract 694). However, these patients were enrolled in clinical trials and thus must have had relatively well-controlled psychiatric comorbidity.

Do HCV Viral Kinetics During DAA Therapy Matter?

The antiviral potency of current interferon alfa–free regimens has negated the predictive value of on-treatment HCV RNA kinetics in determining treatment course or outcome when evaluated in HCV monoinfection. Based on limited data, similar SVR rates are obtained with DAA therapies in individuals with HIV/HCV coinfection, yet to date no detailed data have been presented regarding on-treatment viral kinetics and outcomes in those with HIV/HCV coinfection taking regimens that contain more than 1 DAA drug. Several studies examined the predictive value of on-treatment HCV viral response in HIV/HCV coinfection.

An analysis of more than 2000 HCV-monoinfected and 60 HIV/HCV-coinfected patients treated with paritaprevir/r, ombitasvir, and dasabuvir with or without ribavirin for 12 weeks or 24 weeks compared the viral kinetics of HCV-infected patients with those of HIV/HCV-coinfected patients (Abstract 147). On-treatment viral kinetics were assessed by time to undetectable or detectable (but below the limit of quantification) HCV RNA and correlated with baseline characteristics and treatment outcomes (SVR12). Viral kinetics were similar between HCV-monoinfected and HCV/HIV-coinfected patients, with high SVR rates in both groups regardless of time to viral suppression. Of note, 100% of HIV/HCV-coinfected subjects had viral loads below the limit of quantification by week 4 of therapy. The only baseline factor associated with time to viral suppression was baseline viral load (higher viral load resulted in a longer time to viral suppression).

The predictive value of on-treatment HCV viral load monitoring was also evaluated in an analysis of 67 treatment-naive HCV-monoinfected or HIV/HCV-coinfected patients receiving ledipasvir plus sofosbuvir in the SYNERGY and ERADICATE studies (Abstract 689). A real-time polymerase chain reaction (RT-PCR) assay (Abbott, Abbott Park, IL) and an assay that measured HCV RNA in patients' blood (COBAS TaqMan HCV Test v1.0; Roche, Indianapolis, IL) were used. At week 4, 64% (43/67) of patients had detectable HCV RNA level by RT-PCR (22% [15/67] were quantifiable), and 27% (17/62) had detectable HCV RNA level in blood. At end of treatment, 18% (12/66) of patients had detectable but unquantifiable HCV RNA level by RT-PCR and none had detectable HCV RNA in blood. Only 1 patient experienced relapse after treatment. This analysis highlights the difference in detection thresholds between HCV viral load assays. Unlike the viral load responses seen in the peginterferon alfa era, low-level, detectable, on-treatment HCV viral loads at week 4 do not appear to predict DAA treatment failure, nor does HCV RNA detected below the limit of quantitation at end of treatment.

On-treatment viral kinetics do not determine treatment outcomes with newer, potent DAA regimens for HCV monoinfection or HIV/HCV coinfection.

Collectively, these data reinforce the notion that on-treatment viral kinetics are not useful for determining treatment outcomes with new, potent, interferon alfa–free DAA regimens for HCV monoinfection or HIV/HCV coinfection. This is a departure from viral load monitoring of patients taking interferon alfa–based therapies. However, a high on-treatment HCV viral load may indicate a lack of adherence. Thus, consistent with current guideline recommendations, viral load monitoring may be useful as a surrogate for adherence and may be prudent at select time points during HCV therapy.

Complications of HCV Infection

HCV/HIV coinfection has been associated with more-rapid progression of liver fibrosis and an elevated risk of complications such as renal insufficiency. However, it is unclear the extent to which effective antiretroviral therapy mitigates these complications.

In a North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) analysis of more than 34,000 HIV-infected adults with HCV or hepatitis B virus (HBV) coinfection, the overall rates of end-stage liver disease (ESLD) remained the same in the early (1996-2000), middle (2001-2005), and modern (2006-2010) antiretroviral treatment eras. ESLD rates remained markedly elevated, with a 6- and 7-fold increase in adjusted risk for HIV/HBV and HIV/HCV coinfection, respectively, compared with HIV monoinfection. Individuals with HIV/HCV/HBV coinfection were at highest risk for ESLD (Abstract 638).

To facilitate identifying those with elevated risk for hepatic complications, investigators from the EuroSIDA study reported a prognostic score that more accurately predicted liver-related death than fibrosis staging alone for HIV/HCV coinfection. This emphasizes the importance of clinical factors that contribute to hepatic morbidity and mortality, such as HBV coinfection, duration of HCV infection, and CD4+ cell count (Abstract 637). Female sex has been associated with slower fibrosis progression in HCV-monoinfected patients, but similar rates of fibrosis progression were seen in HIV-infected women and men in the ICONA (Italian Cohort of Antiretroviral-Naive Patients) study (Abstract 636).

Marijuana use has also been associated with liver fibrosis in HCV monoinfection in cross-sectional analyses. However, a large US cohort of HIV/HCV-coinfected women found no association between cannabis use and fibrosis progression. Of note, alcohol use was associated with marijuana use and independently associated with fibrosis progression (Abstract 639).

HCV-monoinfected veterans in the ERCHIVES (Electronically Retrieved Cohort of HCV-Infected Veterans) study database had a substantially increased overall risk of and accelerated time to chronic kidney disease (stage 3-5) after HCV antibody seroconversion than HCV-uninfected individuals, over a mean 5 years to 6 years of follow-up (Abstract 642). These data indicate that despite the availability of effective, less toxic antiretroviral therapy, HIV-infected patients remain at increased risk for accelerated fibrosis and liver-related complications.

Impact of Curative Therapy (SVR) on Clinical Outcomes

SVR has been associated with hepatic, nonhepatic, and mortality-related benefits. In an analysis of US veterans, SVR was associated with a substantially reduced risk of all-cause mortality in HIV/HCV-coinfected and HCV-monoinfected patients (Abstract 656). HCV-monoinfected patients with SVRs had a substantially reduced rate of hepatic decompensation, and there were no hepatic decompensations among HIV/HCV-coinfected patients who attained an SVR. SVR was also associated with substantial improvements in fibrosis measured by noninvasive markers in this study, and substantial reductions in liver stiffness measured by transient elastography and portal pressure measured by invasive hepatic venous pressure gradient in a Spanish cohort of HIV/HCV-coinfected patients (Abstract 657). In an Italian study, SVR was not associated with a substantial reduction in the incidence of diabetes, chronic kidney disease, cardiovascular disease, or death; however, the smaller sample size may have limited power for these endpoints (Abstract 655).

Impact of HCV Treatment on Immune Activation

Chronic immune activation is a common concern in HIV infection and may lead to long-term negative consequences. Chronic HCV infection may also lead to chronic immune activation, and with the advent of potent, interferon alfa–free treatments it is possible to monitor changes in immune activation during therapy and compare posttreatment profiles of patients.

C-X-C motif chemokine 10 (CXCL10; also known as gamma interferon–inducible protein 10 [IP-10]) is an interferon-stimulated chemokine that is consistently elevated in chronic HCV infection, and baseline levels of CXCL10 are predictive of responses to interferon alfa–based therapies. Meissner and colleagues evaluated dynamic changes of total CXCL10 during sofosbuvir-based, interferon alfa–free therapy for HCV infection (Abstract 681). They also measured concentrations of a truncated form of CXCL10, which is a negative regulator of immune activation, and measured activity of the enzyme dipeptidyl peptidase 4 (DPP-4), which catalyzes the cleavage of CXCL10. Consistent with previous studies,[11] they found that CXCL10 levels declined rapidly during HCV therapy in all 30 patients; truncated CXCL10 declined with similar kinetics. DPP-4 levels and activity also decreased but with slower kinetics and substantial decline was only seen by week 20. No difference in decline rates for any isoform was seen between those who achieved an SVR and those who relapsed. At baseline, patients with subsequent relapse did have substantially higher total (long-form plus truncated) and long-form CXCL10 levels.

Immune activation decreases in association with reductions with HCV viral load during effective therapy.

Wilson and colleagues presented data on immune activation in 10 patients with HIV/HCV genotype 1b coinfection with HIV suppression who were treated with an interferon alfa–free HCV regimen of asunaprevir and daclatasvir (Abstract 683). The key finding was that immune activation, measured by expression of HLA-DR + CD38+ in CD4+ and CD8+ T cells, decreased substantially from baseline to day 140 of therapy. CD4+ cell activation decreased by 21% (P = .023) from baseline, and CD8+ cell activation decreased by 12% (P = .018). SVR data and follow-up samples were not presented to assess for increasing immune activation in those patients who relapsed after therapy. Comparisons were also not made to HIV-suppressed patients who were not coinfected with HCV.

These abstracts collectively demonstrate that immune activation decreases in association with reductions in HCV viral load during effective therapy. At this point, studies have been insufficient to determine whether assessments of immune activation before or during therapy may hold some promise for predicting treatment responses to DAA drugs. Treating and curing HCV would certainly seem to be another component to reducing overall immune activation in HIV/HCV-coinfected patients.

Timing of HCV Treatment: Impact of Deferring HCV Therapy

The high cost of HCV therapy combined with the reality of limited medical resources have resulted in the imposition of treatment restrictions based on fibrosis stage in many resource-rich settings. Based on the recognition that those with advanced fibrosis or cirrhosis are most likely to suffer near-term clinical consequences from their HCV-related liver disease, treatment restrictions for those with advanced liver disease have been widely enacted by payers.

Zahnd and colleagues presented modeling data based on fibrosis progression and the clinical endpoints of decompensated liver disease, hepatocellular carcinoma (HCC), and liver-related mortality (Abstract 150). It was assumed that SVR decreased fibrosis progression and development of decompensated liver disease by 10-fold each. HCC risk was estimated to decrease by 2.6-fold following SVR. In the base case scenario, progression to the clinical endpoints over time was evaluated in the Swiss HIV Cohort Study population, assuming a 60% treatment uptake rate and 40% cure rate with peginterferon alfa and ribavirin in HIV/HCV-coinfected patients. These estimates seem optimistic, particularly for treatment uptake with interferon alfa–based therapies. Based on these assumptions, the model predicted a 25% rate of lifetime mortality from HCV-related liver disease.

Transitioning to DAA therapy, the investigators adjusted the uptake rate to 100% and the cure rate to 90%. They then modeled the impact of treatment at various time points and stages—from within 1 month or 1 year of HCV infection to having stage 2 to 4 liver fibrosis. In the model, treating within 1 month or 1 year of infection did not impact outcomes differently, with each resulting in a dramatic reduction in liver-related deaths (to <3%). Modest increases in clinical, liver-related endpoints were seen if therapy was delayed until Metavir fibrosis stage F2; however, the largest increases were seen when therapy was delayed until Metavir fibrosis stage F3 or F4 (rates of HCC and liver-related death in those with Metavir stage F4 were comparable to or higher than those seen with interferon alfa–based treatment). The rates of lifetime liver-related mortality were 25%, 10%, and 5% for treating at Metavir stages F4, F3, and F2, respectively. It was sobering that most deaths in those who had Metavir stage F3 or F4 at the time of treatment occurred after completion of HCV therapy.

It seems obvious that intervention in a disease process at an earlier time point would produce benefits relative to waiting for an advanced disease state to develop, whether it be cardiovascular disease, HIV infection, or malignancies. Following HCV cure, liver disease progression may not immediately halt. Although dramatically diminished, the risk of HCC persists, and other hepatic insults (eg, alcohol use or nonalcoholic steatohepatitis) may continue to push patients to morbid clinical endpoints even after they have been successfully treated. Thus, treating HCV-induced liver fibrosis at an earlier stage would be associated with clinical benefits. However, clinical trial data to support this are lacking and will be difficult and expensive to obtain. In this regard, modeling data can be a useful starting point to attempt to quantitate the impact of HCV cure at various disease stages, despite obvious limitations and inherent assumptions.

HCV Resistance

The clinical relevance of resistance to HCV DAA drugs, owing to preexisting polymorphisms or selection after exposure to an antiviral drug, remains unclear. Much of this undoubtedly relates to the ongoing rapid evolution of therapies themselves and the high efficacy of current DAA therapies that results in few treatment failures in studies. It has been well described that the resistance barrier to DAA drugs may differ between HCV genotype subtypes 1a and 1b.[12]

Cook and colleagues presented a comprehensive overview of NS5A resistance in 109 HCV genotype 1 virus (1a, 71; 1b, 38) samples analyzed by ultra-deep sequencing of virus, with resistant variant detection rates compared with population sequencing (Abstract 696). Variants at NS5A positions 28, 30, 31, 32, 58, and 93 were considered. Frequency and susceptibility of commonly detected resistance-associated variants (RAVs) was assessed in a phenotypic assay using HCV genotype 1a and 1b replicons. Consistent with prior studies, NS5A RAVs were detected more frequently in samples of HCV genotype 1a than in genotype 1b, with 38% (27/71) of genotype 1a viruses harboring NS5A RAVs compared with 21% (8/38) of genotype 1b viruses. RAVs at position 28 were most frequent in HCV genotype 1a viruses, and position 93 RAVs were most frequently seen in genotype 1b.

The resistance barrier to DAA drugs may differ between HCV genotype subtypes 1a and 1b.

In addition to an impact on prevalence, the phenotypic impact on susceptibility to NS5A inhibitors also tends to be larger in HCV genotype 1a than in 1b. This observation was borne out in the phenotypic assay results presented, in which the average fold-change in 50% inhibitory concentration of an NS5A inhibitor was approximately 10-fold higher for RAVs in HCV genotype 1a backbone (average fold increase of >150 in genotype

Table 3. HCV Direct-Acting Antiviral Drug Classes and US FDA Approval Status

HCV Direct-Acting Antiviral Class	Drug (year/status of US FDA approval)
NS3 Protease inhibitors	Simeprevir (2013) Paritaprevir/ritonavir (2014) Asunaprevir (not approved)
NS5B Nucleos(t)ide polymerase inhibitor	Sofosbuvir (2013)
NS5B Nonnucleoside polymerase inhibitors	Dasabuvir (2014) Beclabuvir (not approved)
NS5A Inhibitors	Ledipasvir (2014) Ombitasvir (2014) Daclatasvir (not approved)

Abbreviations: HCV, hepatitis C virus; NS, nonstructural protein; US FDA, US Food and Drug Administration.

1a vs an average fold increase of <20 in genotype 1b). In clinical practice, only population sequencing results will be available; however, in this study, population sequencing only detected RAVs in 31% of the samples in which RAVs were detected through ultradeep sequencing. A clinically significant threshold for RAV prevalence in quasispecies has not yet been determined.

As preferred HCV regimens evolve, the necessity of determining the presence of a baseline Q80K RAV, which is associated with decreased response to simeprevir, is likely to continue to wane. However, accurate determination of HCV genotype subtype remains crucial to determining the components (whether to include ribavirin) and durations of newer interferon alfa–free treatments.

Joy and colleagues presented data on NS3 deep sequencing of 376 clinical samples of HCV genotype 1 in British Columbia, Canada, to determine Q80K-related resistance status (Abstract 697). The most interesting results from this study were not the data on Q80K prevalence—this was much higher in HCV genotype 1a than in 1b, as expected—but rather the striking number of instances of incorrect subtyping or of inability to determine subtype using a line probe genotype assay, which was resolved using deep sequencing. Ninety-six percent (52/54) of HCV genotype 1 samples whose subtype had not been determined were classified as genotype 1a using NS3 deep sequencing, as were 44% (28/91) of samples previously categorized (using the line probe assay) as genotype 1b. Although using deep sequencing to determine genotype subtype is impractical for patient care, these results suggest that clinicians who receive a genotype testing result indicating that HCV genotype 1 cannot be subtyped should treat these patients as genotype 1a. This is already a conservative approach, as treatment regimens for HCV genotype 1a are longer in duration or include ribavirin in some DAA regimens in select situations. Of course, it is unclear whether this finding is widely applicable or a unique phenomenon in HCV genotype 1 viruses circulating in British Columbia. The 11% prevalence rate of the Q80K mutation in samples of HCV genotype 1b determined using the line probe assay is higher than that seen in other studies examining genotype 1b isolates using the same assay, suggesting the assay may be particularly prone to incorrect subtyping for HCV genotype 1 viruses circulating in British Columbia or that perhaps a higher prevalence of genotype 1b isolates in British Columbia do harbor the Q80K mutation.

Screening for HCV

Recommendations for birth cohort screening for HCV have been in place since 2013.[13] These initial recommendations were based on the estimate that roughly 75% of HCV-infected individuals in the United States were born between 1945 and 1965. Using data from a large, national clinical laboratory, Klevens and colleagues presented data on the use of FIB-4 score to quantify the frequency of HCV-related advanced liver disease across different age-based cohorts (Abstract 145).Using Using FIB-4 score as a surrogate for liver disease staging (advanced fibrosis and cirrhosis categorized as FIB-4 scores of 2.0-3.7 and >3.7, respectively), estimates of the proportions of persons with advanced fibrosis or cirrhosis were presented for different age groups. As expected, the proportion of persons with advanced fibrosis or cirrhosis increased based on age, ranging from 11% in those born after 1965 to almost 75% in those born before 1945. Within the birth cohort of those born between 1945 and 1965, 47% of persons were estimated to have advanced fibrosis or cirrhosis; perhaps more importantly, persons in this birth cohort account for 81% of cases of advanced fibrosis or cirrhosis in the United States.

HCV-infected individuals born between 1945 and 1965 account for 81% of cases of advanced fibrosis in the United States.

Available data suggest that uptake of birth cohort HCV screening has been limited among primary care practitioners. In 2 abstracts presented by Brodsky and colleagues (Abstract 658) and Tzarnas and colleagues (Abstract 668), respectively, investigators first assessed practitioner knowledge of current HCV therapeutics and screening recommendations and then evaluated the impact of educational and electronic medical record (EMR)-based prompts to improve screening approaches and coverage. In a practice-level survey of 7 primary care practices, including 57 primary care practitioners and 42 clinic support staff members, investigators found that knowledge of current HCV treatment efficacy and durations was poor (Abstract 658). Only 40% of practitioners were aware that cure rates of greater than 70% were attainable for HCV infection, and slightly more than 60% of practitioners were able to identify recommended treatment duration ranges. HCV screening in line with Centers for Disease Control and Prevention (CDC) and US Preventive Services Task

Force (USPSTF) recommendations[13,14] was poor despite a reasonable level of awareness of testing guidelines (68%). Modest improvements in frequency of HCV screening with education and EMR prompts based on birth cohort were seen over time, although no site increased testing by more than 50% of the targeted population within 2 months of implementing an EMR prompt system.

In the second abstract, a more detailed description and analysis of the impact of an educational and EMR prompt–based approach were presented. Before education and EMR prompting, only 7% of eligible persons were screened. Institution of the EMR prompt program increased this rate to 18% to 20%, suggesting some effectiveness but highlighting the fact that other approaches to increase HCV screening in primary care are needed. Persistent perceptions of a lack of efficacy of HCV therapy or concerns that it will not be covered for many patients (owing to payer limitations) may contribute to the lack of widespread HCV screening. It is encouraging that modification of HCV screening orders in EMRs did have a dramatic effect on facilitating appropriate testing. Identification of individuals with HCV infection who are already linked to care is key to realizing the benefits of improvements in HCV therapy. Clearly, additional education of practitioners and clinic staff on HCV testing guidelines and advancements in therapy are needed.

Other data presented at CROI 2015 also support the notion that widespread adoption of CDC/USPSTF HCV screening guidelines has not yet occurred in clinical practice. In a CDC-funded project in Washington, DC, only 31% of more than 4000 eligible persons were screened for HCV during a 2-year study (Abstract 666). Of concern, a higher than expected HCV seroprevalence rate of 7.5% was found, including 13% in black men within the cohort. In a complementary emergency department (ED)-based study conducted in Baltimore, Maryland, all patients who had blood drawn in the ED were tested for HCV antibody (samples were de-identified) to assess the impact of CDC recommendations for HCV testing (Abstract 667). Over 8 weeks 4713 ED patients were tested for HCV; seroprevalence rate was 13.8%, with approximately two-thirds of those patients having previously diagnosed HCV infection. Although adding CDC recommendations for birth cohort screening to risk-based screening increased HCV detection 2-fold, up to 25% of unknown HCV infections would still have been missed. These findings suggest that routine screening of all persons presenting to the ED may be of value in settings with higher HCV prevalence rates, such as most urban EDs.

HCV Prevalence and Linkage to Care

Two studies highlighted the substantial prevalence of HCV infection and the many practical hurdles that remain for integrating HCV therapy into the care of poorer, generally minority populations in urban settings. In a longitudinal study of HIV-seropositive persons in care at 1 of 13 centers in Washington, DC, a high HCV prevalence rate of 13.3% was documented, including a remarkable incidence of 1.56 HCV infections per 100 person-years (Abstract 660). Following guidance from the American Association for the Study of Liver Diseases/Infectious Diseases Society of America/International Antiviral Society–USA (AASLD/IDSA/IAS–USA) Recommendations for Testing, Managing, and Treating Hepatitis C on which patients should be prioritized for HCV therapy (http://www.hcvguidelines.org),[15] more than 70% of patients in the study had factors placing them at high priority for HCV therapy (22% had evidence of advanced fibrosis or cirrhosis).

Data from community-based HCV testing and linkage-to-care programs in San Diego, California, identified a similarly high rate of HCV prevalence in at-risk, vulnerable populations and showed a drop-off in treatment rates associated with lack of insurance and medication coverage (Abstract 661). Of 1634 persons tested, 18% were HCV seropositive. In a traditional assessment of linkage to care and HCV treatment, 94% of persons had an HCV RNA performed (likely reflecting point-of-care HCV antibody testing with reflex phlebotomy) and 71% had a positive HCV RNA result. Despite this, only 45% of individuals were linked to care and only 7% of those initiated HCV therapy. Failure to link individuals to care and lack of insurance coverage for HCV therapy were major barriers to treatment.

Acute HCV Infection

HIV-infected men who have sex with men (MSM) are increasingly recognized as being at risk for HCV infection and for reinfection after HCV treatment. In an important reminder of this risk, an observational German study of 212 HIV-infected MSM with acute HCV infection reported that 14.6% of participants were subsequently reinfected with HCV after cure or spontaneous viral clearance. Injection drug use, with ever injected drugs reported at 36%, and sexual exposure were risk factors for HCV transmission (Abstract 671). Spontaneous viral clearance occurred in 10% of participants. The IPERGAY study of preexposure prophylaxis (PrEP) reported 4 acute HCV infections, a reminder that men at risk for HIV infection should be counseled on the risk of sexually acquired HCV as well (Abstract 23LB). In addition, prescribers of PrEP should be vigilant about the possibility of acute HCV infection as well as other sexually transmitted infections.

MSM are increasingly recognized as being at risk for HCV infection and for reinfection after HCV treatment.

In a cohort of men newly diagnosed with HIV infection in Los Angeles, California, more than half of whom were recently infected, prevalence of HCV coinfection was low (1.6%) at the time of HIV diagnoses (Abstract 672). This suggests that HCV infection may be occurring after HIV infection in some MSM, highlighting the opportunities for targeted counseling and HCV prevention strategies for MSM newly diagnosed with HIV infection. In

Amsterdam, a case-control study of acute HCV infection in HIV-infected patients identified sexual risk behaviors for HCV acquisition: receptive unprotected anal intercourse, sharing of sex toys, a recent ulcerative sexually transmitted infection, and unprotected fisting. Nonsexual risk factors were injection drug use, sharing of noninjection drug equipment (ie, straws), and lower CD4+ cell count (Abstract 674). Modeling by the Swiss HIV Cohort Study predicts that even with widespread implementation of effective HCV therapy, stabilization or reduction in high-risk sexual behaviors will be necessary in order to curb the HCV epidemic (Abstract 675).

With regard to treatment of acute HCV infection, 12 weeks of boceprevir with peginterferon alfa and ribavirin resulted in an SVR12 rate of 76% (26/34) in HIV-infected patients with acute HCV infection (treatment initiated within 26 weeks of infection), indicating that treatment duration with an HCV PI and peginterferon alfa can be cut in half and still maintain the same response rates (Abstract 669). Whether shortened courses of all-oral DAA therapy can be used to effectively treat acute HCV infection is unknown but is under investigation.

HCV Recurrence After HCV Therapy

In a meta-analysis of 49 studies and more than 8000 participants, risk of HCV infection recurrence varied by risk categorization and HIV serostatus. Participants categorized as having high risk included injection drug users and those who were incarcerated; categorization as low risk excluded those with HIV coinfection, injection drug users, and those who were incarcerated. Data on sexual risk for HCV reinfection were not presented. The 5-year risk of HCV infection recurrence was 1.14% among low-risk HCV-monoinfected patients, 13.2% among high-risk HCV-monoinfected patients, and rose to 21.7% among HIV/HCV-coinfected patients. Given the association with elevated risk, recurrent HCV infection was largely attributed to reinfection rather than late relapse (Abstract 654). In 8 National Institutes of Health studies of sofosbuvir and ribavirin or sofosbuvir plus ledipasvir in HCV-monoinfected and HIV/HCV-coinfected patients, 100% of patients who attained an initial SVR12 remained free of HCV infection during an average 35 weeks of follow-up, with the exception of one phylogenetically confirmed reinfection (Abstract 653). These data reinforce SVR12 as a biomarker for long-term HCV cure and are a sobering reminder that patients cured of HCV infection remain at risk for re-infection, with HIV/HCV-coinfected patients having a markedly higher risk.

Other Viral Hepatitides

HBV Vaccination Strategy in HIV Infection

Attaining protective antibody titers with HBV vaccination is an ongoing challenge for many HIV/HBV-coinfected patients. Among HIV-infected patients with CD4+ counts greater than 200 cells/μL who did not respond to initial HBV vaccinations, revaccination with a double dose of HBV vaccine did not significantly increase hepatitis B surface antibody (HBsAb) response compared with a standard dose (67% vs 74%, respectively; $P = .2$) in a randomized clinical trial (Abstract 701). However, double-dose vaccination was associated with high HBsAb titers (>100 IU/mL) and with a protective response 72 weeks after vaccination. CD4+ cell count was not associated with increased response to vaccination. Double-dose HBV vaccination has been associated with higher seroconversion rates in some studies,[16] particularly with CD4+ counts greater than 350 cells/μL.[17] Although it did not demonstrate an increase in overall seroconversion rates, this study indicates there may be a benefit of longer duration or higher titers in those who respond to the double-dose vaccine strategy.

Hepatitis Delta Virus and Hepatitis E Virus

Hepatitis delta virus (HDV) and hepatitis E virus (HEV) are relatively uncommon viral coinfections of HIV; however, both can cause serious hepatic disease and may go unrecognized. HDV viremia was present in 2 of 138 HIV/HBV-coinfected patients in Ohio (Abstract 707). Although the overall rate of HDV prevalence was low among these patients, HDV was not suspected in the 2 patients who had it, suggesting that HDV infection may go undiagnosed in some US populations. Identification of HDV is clinically important, as it is associated with more-rapid disease progression and may respond to treatment. In a double-blind phase IIa study, use of the investigational oral prenylation inhibitor lonafarnib caused a substantial decline in HDV RNA levels during 28 days of therapy in HDV-infected patients without HIV coinfection (Abstract 708LB). Lonafarnib may be a promising alternative to interferon alfa, which is poorly tolerated and has suboptimal efficacy for HDV treatment.

Investigating the incidence and clinical impact of HEV infection among HIV-infected patients, a prospective Spanish study found that 5% of patients developed HEV infection during a median 12 months of follow-up. HEV seroconversion was associated with clinical symptoms in 58% of patients, including fever and abdominal pain. Compared with HIV-infected patients without HEV infection, HIV/HEV coinfection was associated with a significant increase in transient HIV viremia (35.0% vs 3.8%, respectively; $P < .001$) and frank hepatic decompensation in patients with cirrhosis (33.3% vs 2.1%, respectively; $P < .001$) (Abstract 709).

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All cited abstracts appear in the CROI 2015 Program and Abstracts eBook, available online at www.CROIconference.org.

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