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SUPPLEMENT ARTICLE

Management of Hepatitis C/HIV Coinfection in the Era of Highly Effective Hepatitis C Virus Direct-Acting Antiviral Therapy

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The increased life expectancy of persons infected with human immunodeficiency virus (HIV) treated with antiretroviral therapy (ART) has resulted in renewed attention to non-HIV-related diseases exacerbated by HIV infection. Coinfection with hepatitis C virus (HCV) is a particular area of concern, as the global prevalence has been estimated at 2.5–5 million people. In this article, we discuss the epidemiology of HCV infection and reinfection, HCV-related liver disease progression in the era of effective ART, and the efficacy of emerging HCV treatment strategies in persons with HIV/HCV coinfection. New data regarding treatment of persons with HIV/HCV coinfection suggest that HCV treatment should be a priority in those with HIV. Results from recent studies using all-oral HCV regimens have shown high rates of sustained virologic response in both clinical trials and real-world settings. A multidisciplinary approach to HCV treatment in those with HIV is recommended for optimal patient management. Following HCV cure, practitioners also need to be mindful of the risks for HCV reinfection and educate patients on protective measures.

Keywords. HCV; hepatitis C; HIV; HIV/HCV coinfection; direct acting-antivirals (DAAs).

Antiretroviral therapy (ART) has markedly improved the life expectancy of persons infected with the human immunodeficiency virus (HIV), which in some settings now approaches that of the general population [1–3]. The longer life spans of those infected with HIV have resulted in a renewed focus on non-HIV-related diseases that may be exacerbated by concurrent HIV infection [1]. A particular area of concern is coinfection of HIV with the hepatitis C virus (HCV), as both share common routes of transmission. For example, coinfection with chronic HCV is found in 10%–30% of all patients with HIV infection and in as many as 90% of HIV-infected persons who inject drugs [4–7]. Overall, the global prevalence of HIV/HCV coinfection has been estimated at 2.5–5 million people [8]. Additionally, the natural history of HCV-related liver disease progression is accelerated in patients with HIV. This leads to a more rapid progression of liver fibrosis as compared to those infected with HCV alone [9–11], and results in HCV-related liver complications including hepatic decompensation [12]. As a result of longer life expectancy coupled with prevalent and progressive HCV disease, liver disease due to HCV has emerged as the leading non-HIV cause of death in many regions [13].

The purpose of this review is to discuss the epidemiology of HCV infection and reinfection, HCV-related liver disease progression in the era of effective ART, and the efficacy of emerging HCV treatment strategies in persons with HIV/HCV coinfection. Drug interactions between antivirals used to treat HIV and those used to treat HCV are also common and are the subject of a companion review article in this issue [14].

LIVER DISEASE PROGRESSION IN HIV/HCV-COINFECTED PATIENTS

Despite advances in HIV treatment and overall longer life spans, liver disease remains a prominent cause of mortality in those with HIV. The results of a recent observational study of trends over time in all-cause and disease-specific mortality in people with HIV from 1999 to 2011 suggested that death rates in those with HIV and access to antiviral therapy decreased starting in 1999–2000 [15]. The occurrence of deaths attributable to liver disease showed a >50% reduction; however, results also indicated that of the 3909 individuals who died during the study period (N = 49 731), 13% of all deaths (n = 515) were attributable to liver disease. The majority of liver deaths were due to viral hepatitis (87% of liver-related deaths and 11% of all observed deaths). Of note, effective HCV treatment with direct acting-antivirals (DAAs) was not available during the study period [15].

Advances in ART have had a significant impact on reducing HIV-related deaths. In this context, there has been greater recognition of the adverse effects of HIV infection on other organ systems and diseases. For example, despite effective ART, patients with HIV are more likely to develop, or even die from,

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cardiovascular disease, liver disease, and certain types of cancer compared with those of similar age and sex who are not HIV infected [16–18]. Researchers hypothesize that HIV infection accelerates the biological effects of aging through chronic immune activation leading to the premature presentation of disease states, such as cardiovascular and liver diseases, typically seen at older ages in persons without HIV infection [19–21]. With respect to HCV disease, several studies have been published supporting the assertion that liver disease is accelerated by HIV infection. A recent study of a cohort of 1176 people with HCV was conducted to determine whether HIV reduced the age at which liver disease occurred, as well as to investigate other correlates of liver fibrosis [22]. Cohort participants were all infected with HCV, and 34% were coinfected with HIV; all were followed prospectively with liver elastography to determine liver disease progression. Study results revealed that the prevalence of significant fibrosis without cirrhosis was 12.9% in HIV/HCV-coinfected participants as opposed to 9.5% in those with HCV alone. Similarly, HIV/HCV-coinfected persons had significantly higher rates of cirrhosis than those with HCV only (19.5% vs 11.0%, respectively). After adjusting for increasing age, HIV infection, daily alcohol use, chronic hepatitis B virus infection, body mass index >25 kg/m^2, and greater plasma HCV RNA levels, all of which were independently associated with liver fibrosis, those with HIV coinfection showed liver fibrosis measurements that were equal to those of non-HIV-infected individuals who were older by an average of 9.2 years. These results strongly suggest that age and HIV/HCV coinfection adversely impact the progression of HCV. The study authors noted that their findings were consistent with the hypothesis that both HIV infection and older age promote HCV-related liver disease progression, and speculated that their findings may be reflective of common mechanisms, although the mechanism(s) responsible for the effects of HIV infection and aging on the progression of liver fibrosis remain to be elucidated [22].

Although the study by Kirk et al demonstrated convincingly that differences exist between HIV/HCV-coinfected individuals and HCV-monoinfected individuals regarding liver fibrosis progression [22], the study did not examine the relationship between HIV coinfection and rates of hepatic decompensation, hepatocellular carcinoma (HCC), and liver-related death in HIV/HCV-coinfected patients on ART vs HCV-monoinfected patients. This question was examined in a subsequent study conducted by Lo Re and coworkers in 4280 HIV/HCV-coinfected patients who initiated ART between 1997 and 2010 and 6079 HCV-monoinfected patients receiving care through the Veterans Affairs health system during the same time period [23]. The aim was to compare the incidence of hepatic decompensation between ART-treated HIV/HCV-coinfected and HCV-monoinfected patients to test the hypothesis that decompensation rates would remain higher in those patients who were coinfected compared to those with HCV alone independent of ART. Although ART was associated with a decreased incidence of hepatic decompensation events compared with coinfected patients not receiving antiretrovirals, the ART-treated HIV/HCV-coinfected patients still had greater rates of hepatic decompensation and severe liver events compared with HCV-monoinfected patients. The study data supported the assertion that the risk for hepatic decompensation events decreased further the longer patients had been on ART prior to initiation of the study. This increased risk of liver decompensation was not fully ameliorated by suppression of HIV replication in patients with HIV RNA levels <400 copies/mL over the median follow-up period of 6.8 years. Although effective treatment of HIV with ART is beneficial and should be prioritized in patients with HIV/HCV coinfection, HIV treatment alone is inadequate for equalizing rates of end-stage liver disease development between HIV-infected and -uninfected patients with HCV. Other factors that were associated with higher rates of decompensation among coinfected patients on ART included baseline advanced hepatic fibrosis, baseline hemoglobin <10 g/dL, diabetes mellitus, and non–African American race. The study authors pointed out that specific mechanisms underlying the higher rates of hepatic decompensation in coinfected patients on ART remained unknown [23]. Despite this, it is important to note that an additional analysis by this same research group suggests that patients continue to accrue benefits of ART on slowing the rate of fibrosis progression with longer durations of HIV treatment [24]. Finally, once hepatic decompensation occurs, HIV-coinfected patients also die at a faster rate than HCV-monoinfected persons [25]. Taken together, these results indicate that the adverse effects of HIV coinfection on HCV disease are reduced but not fully reversed with effective HIV treatment, underscoring the need for effective, curative HCV treatment in patients with HIV/HCV coinfection.

The benefit of HCV cure was demonstrated in a meta-analysis by Simmons and colleagues on the relationship of HCV treatment outcomes and survival reported in 31 studies involving a total of 33 360 patients with HCV and HIV/HCV coinfection [26]. The analysis was focused on the survival benefit of achieving HCV cure or sustained virologic response (SVR; defined as an undetectable level of HCV RNA 24 weeks following the termination of therapy). Achieving SVR was accompanied by an approximately 50% reduction in the risk of all-cause mortality compared with not achieving an SVR. The decreased risk of all-cause mortality was even higher for the cirrhotic population (74%), and higher still for the coinfected population (79%). These data describing decreases in risk of all-cause mortality were accompanied by the observation of much lower liver-related mortality rates at 5 years for those who achieved SVR compared with those who did not. The survival benefit associated with SVR was similar in persons with and without HIV coinfection [26]. Unfortunately, in the era of interferon-based HCV

treatment, relatively few patients with HIV/HCV coinfection achieved SVR and, although successfully treated individuals derived clinical benefit, the impact on a population level was minimal [27]. Despite the substantial positive impact of SVR on HCV-related morbidity and mortality, it is important for practitioners to remember the need for continued HCC screening in patients with cirrhosis following SVR [28]. Pending additional data, screening for HCC with ultrasound every 6 months is recommended indefinitely [29].

EFFICACY OF DAA THERAPIES IN COINFECTION

In the era of interferon alfa–based HCV treatments, multiple studies demonstrated that SVR rates were markedly lower in patients with HIV/HCV coinfection, compared to those with HCV alone [30–32]. In addition, the treatment of HCV in HIV-infected persons was complicated by poor tolerability and frequent treatment-limiting adverse effects. Not surprisingly, few HIV/HCV-coinfected patients were able to achieve SVR with interferon alfa–based treatments [32]. Antivirals are now in use that directly target HCV enzymes and proteins. They are used in combination to provide oral, interferon-free regimens to patients with chronic HCV infection. In stark contrast to the experience with interferon, these DAA HCV treatment regimens have been highly effective in persons with HIV/HCV coinfection (Table 1).

Naggie et al investigated the potential of DAAs as a viable treatment option in persons coinfected with HIV and HCV. To accomplish this, they conducted the ION-4 study, a multicenter, single-arm, open-label study of 335 HIV patients coinfected with HCV genotype 1 or 4 [38]. All subjects were receiving ART including tenofovir and emtricitabine combined with either efavirenz (48%), rilpivirine (9%), or raltegravir (44%). As for prior HCV treatment, 55% were treatment experienced, including 53 subjects previously treated with an HCV protease inhibitor (plus peginterferon alfa [PEG]/ribavirin [RBV]) and 14 previously treated with sofosbuvir (SOF) plus RBV. One-fifth (20%) also had cirrhosis. Study patients were administered an NS5A inhibitor (ledipasvir [LDV]), and an NS5B nucleotide inhibitor (SOF), as a single fixed-dose combination for 12 weeks. The majority of patients (82%) were male, 34% were African American, and almost all patients (98%) were genotype 1, with a majority of those (75%) being genotype 1a. The results were extraordinarily positive: 96% of the 322 patients were HCV RNA negative at 12 weeks after the end of therapy (SVR_{12}). High SVR_{12} rates (≥94%) were observed for key subgroups (treatment naive and experienced, with or without cirrhosis). When assessed by HCV genotype, the data demonstrated SVR_{12} of 96%, 96%, and 100% for those with HCV genotypes 1a, 1b, and 4, respectively. A relatively small number of patients (13) did not attain SVR_{12}, and 10 experienced a relapse at the end of the treatment phase. All of the relapsed patients were African American, resulting in a lower SVR rate (90% [95% confidence interval, 83%–95%]) for this group. Eight of the African American patients were taking efavirenz as part of their HIV treatment regimen. While a precise explanation for the lower responses seen in this group of African Americans has not been found, exposure to LDV did not significantly differ between this group and the overall study population [38].

No confirmed HIV type 1 (HIV-1) virologic rebound was detected. None of the patients discontinued treatment due to adverse events (AEs), the most common of which were headache (25%), fatigue (21%), and diarrhea (11%). Two percent of all participants experienced serious AEs, and 1 person died of non-treatment-related causes after treatment discontinuation during the study period. Because regimens including tenofovir disoproxil fumarate (TDF) have been linked to tenofovir-associated renal injury and the potential for SOF and LDV to further increase tenofovir exposure [39], estimated creatinine clearance was measured in this study as a proxy safety measure for renal function. Creatinine levels did not differ significantly among the ART regimens on study. Four patients (1%) demonstrated a change in creatinine ≥0.4 mg/dL over the course of the study, and of these, 2 completed treatment with no ART change, 1 had a TDF dose reduction, and 1 discontinued TDF treatment. The results of this study provide strong support for the use of SOF/LDV in treating HCV genotype 1 (and 4) in persons with HIV [38].

The ALLY-2 trial also assessed the efficacy and safety of the combination of an NS5A inhibitor (daclatasvir) and an NS5B inhibitor (SOF) in an open-label study involving 151 patients infected with HIV who had not received prior HCV treatment, as well as 52 patients who were HCV treatment experienced [40]. Almost all patients in the study (98%) were receiving ART for the treatment of their HIV. Those patients naive to HCV treatment were randomized in a 2:1 ratio to receive daclatasvir at a standard dose of 60 mg daily (with dose adjustment for concomitant ART: to 30 mg in patients receiving ritonavir-boosted protease inhibitors and to 90 mg in those receiving efavirenz or nevirapine) in addition to 400 mg of SOF daily for either 12 or 8 weeks. Patients who were HCV treatment experienced also received 12 weeks of therapy at the same doses. Inclusion criteria included HCV genotype 1–6 (although only persons with genotypes 1–4 were enrolled), and a $CD4^+$ count ≥100 cells/μL in ART-treated patients and ≥350 cells/μL in those not on ART. Additionally, most common ART regimens were allowed during the course of the study. The majority of patients (87%) were male, 34% were African American, 83% carried HCV genotype 1, and 69% of those carried HCV genotype 1a. Six percent of the overall study population was infected with HCV genotype 3, and 14% had cirrhosis. Study results indicated that high SVR_{12} rates were achieved using this combination for 12 weeks. Previously untreated patients infected with HCV genotype 1 demonstrated an SVR_{12} rate of 96.4% after 12 weeks of treatment, and 75.6% when treated for 8 weeks.

Table 1. Sustained Virologic Response Rates From Clinical Trials Investigating the Efficacy of Direct-Acting Antiviral Therapies in Human Immunodeficiency Virus/Hepatitis C Virus Coinfection

Study Name	Type and No. of Patients	ARV Allowed	SVR Rates	Adverse Events	Reference
PHOTON-1	223 patients enrolled Treatment naive GT 1: 114 • 4.4% cirrhosis GT 2 and 3: 68 • 10.4% cirrhosis Treatment experienced GT 2 and 3: 41 • 24.4% cirrhosis	212 of 223 patients were on ARV therapy. The following agents were allowed: TDF + FTC, EFV, ATV/r, DRV/r, RAL, RPV, other	Treatment naive 76% GT 1 88% GT 2 67% GT 3 Treatment experienced 92% GT 2 94% GT 3	Most common were fatigue, insomnia, headache, and nausea No adverse events on HIV disease or treatment	[19]
PHOTON-2	275 patients enrolled Treatment naive GT 1: 112 • 15% cirrhosis GT 2: 19 • 5% cirrhosis GT 3: 58 • 5% cirrhosis GT 4: 31 • 26% cirrhosis Treatment experienced GT 2: 6 • 33% cirrhosis GT 3: 49 • 47% cirrhosis	265 of 275 patients were on ARV therapy. The following agents were allowed: TDF + FTC, EFV, ATV/r, DRV/r, RAL, RPV, other	Treatment naive 85% GT 1 89% GT 2 91% GT 3 84% GT 4 Treatment experienced 83% GT 2 86% GT 3	Most common were fatigue, insomnia, asthenia, and headache One patient experienced HIV viral breakthrough	[20]
ION-4	335 patients enrolled GT 1: 327 GT 4: 8 20% cirrhosis overall	335 (100%) patients were on ARVs consisting of TDF and FTC with EFV, RPV, or RAL	Both treatment naive and experienced 96% GT 1 100% GT 4	Most common were headache, fatigue, and diarrhea	[33]
ALLY-2	203 patients enrolled 151 treatment naive • 101: DCV + SOF for 12 wk ○ 9% cirrhosis • 50: DCV + SOF for 8 wk ○ 10% cirrhosis 52 treatment experienced • 52: DCV + SOF for 12 wk ○ 29% cirrhosis	199 (98%) patients were on ARVs consisting of DRV/r, ATV/r, LPV/r, EFV, NVP, RPV, RAL, or DTG	GT 1:96.4% naive for 12 wk 75.6% naive for 8 wk 97.7% experienced for 12 wk GT 1–497% naive for 12 wk 76% naive for 8 wk 98.1% experienced for 12 wk	Most common were fatigue, nausea, and headache	[11]
C-EDGE COINFECTION	218 patients enrolled GT 1a: 144 GT 1b: 44 GT 4: 28 GT 6: 2 16% cirrhosis overall	211 (97%) patients were on ARVs consisting of ABC, TDF, RAL, DTG, or RPV	96.5% GT 1a 95.5% GT 1b 96.4% GT 4 100% GT 6	Most common were fatigue, headache, and nausea. No patient discontinued treatment because of an AE. Two patients receiving ART had transient HIV viremia.	[34]
C-WORTHY	218 patients enrolled; 59 (arms 7 and 8) were HCV/HIV coinfected Arm 1: GT 1a + 1b;12 wk Arm 2: GT 1a + 1b;12 wk Arm 3: GT 1b; 12 wk Arm 4: GT 1a; 8 wk Arm 5: GT 1a + 1b; 12 wk Arm 6: GT 1a; 12 wk Arm 7: GT 1a + 1b; 12 wk Arm 8: GT 1a + 1b; 12 wk	59 (100%) of coinfected patients were on ARVs consisting of RAL plus 2 nucleoside or nucleotide reverse transcriptase inhibitors	Arm 1: 93% Arm 2: 93% Arm 3: 98% Arm 4: 80% Arm 5: 93% Arm 6: 98% Arm 7: 97% Arm 8: 87%	Most common were mild to moderate fatigue, headache, nausea, and diarrhea.	[35]
ERADICATE	50 patients enrolled	37 (74%) patients were receiving ARVs consisting of TDF/FTC plus EFV, RAL, RPV, RAL plus RPV, or RAL plus EFV	98%	Most common AEs were nasal congestion, myalgia, headache, and fatigue. No participants discontinued study medications due to adverse effects.	[36]
TURQUOISE-I	63 patients enrolled with HCV GT 1 31 with 12 wk of treatment 19% with cirrhosis 32 with 24 wk of treatment 19% with cirrhosis	63 (100%) patients were receiving ARVs consisting of an atazanavir- or RAL-inclusive ARV regimen	94% with 12 wk of treatment 91% with 24 wk of treatment	Most common AEs were fatigue, insomnia, nausea, and headache. No patient had a confirmed HIV-1 breakthrough of ≥200 copies/mL during treatment.	[37]

Abbreviations: ABC, abacavir; AE, adverse event; ART, antiretroviral therapy; ARV, antiretroviral; ATV/r, ritonavir-boosted atazanavir; DCV, daclatasvir; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LPV/r, ritonavir-boosted lopinavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; SOF, sofosbuvir; SVR, sustained virologic response; TDF, tenofovir disoproxil fumarate.

Treatment-experienced patients had an SVR_{12} rate of 97.7%. When assessed by HCV genotype/subtype, 96% of patients with genotype 1a and 100% with genotype 1b, 2, 3, and 4 achieved SVR_{12} following 12 weeks of therapy. In an analysis of HCV genotype 1–infected patients, SVR_{12} rates were found to be 96% for those in the 12-week treatment-naive group, 98% in the 12-week treatment-experienced group, and 76% in the 8-week treatment-naive group. Regarding treatment failures in the 12-week arms only, 1 patient withdrew at week 1, another had detectable HCV RNA at the end of the treatment period, and 2 patients relapsed. Safety and tolerability assessments indicated that 2% of patients experienced serious AEs, although none of the patients discontinued treatment due to AEs, and the investigators determined that no serious AEs were attributable to the study drugs. One patient died by posttreatment week 24 from cardiomyopathy (cause undetermined) and multiorgan failure. Fatigue, nausea, and headache were the most commonly observed AEs, none of which contributed to study discontinuation. It is also important to note that HIV-1 control was not compromised. The results for the use of 12 weeks of daclatasvir and SOF are quite encouraging for both previously untreated and treatment-experienced HCV patients coinfected with HIV [40].

Another recently introduced all-oral regimen combines 3 DAAs: paritaprevir dosed with ritonavir, ombitasvir (coformulated, PrO), and dasabuvir given with (for all patients with genotype 1a infection) or without (for patients with genotype 1b infection) RBV (PrOD). This regimen has resulted in response rates of 92%–100% in patients monoinfected with HCV genotype 1, including traditionally difficult-to-treat patients [33, 41–44]. The 3 agents, ombitasvir, paritaprevir, and dasabuvir, have different mechanisms of action: Ombitasvir is a potent HCV NS5A inhibitor, whereas paritaprevir is a potent inhibitor of NS3/4A protease, and dasabuvir is a nonnucleoside NS5B polymerase inhibitor. To enable once-daily dosing of paritaprevir, it is necessary to coadminister it with a low dose of the pharmacokinetic enhancer ritonavir (paritaprevir/r); paritaprevir, ritonavir, and ombitasvir have been coformulated in a single tablet for ease of dosing. The TURQUOISE-I trial was conducted to assess the efficacy and safety of this PrOD regimen in HIV/HCV genotype 1–coinfected individuals [37]. This randomized, open-label study was designed to define the AE profile and measure the virologic outcomes of the PrOD regimen with RBV for 12 or 24 weeks in 63 treatment-experienced or treatment-naive patients coinfected with HCV genotype 1. Inclusion criteria consisted of a $CD4^+$ count ≥200 cells/μL or a $CD4^+$ percentage ≥14%, and plasma HIV-1 RNA suppression (<40 copies/mL) while taking a stable ART regimen that included atazanavir or raltegravir. Importantly, HIV/HCV genotype 1–coinfected individuals with prior PEG/RBV treatment experience and with cirrhosis were also included in the study population. In a 1:1 ratio, patients were randomized to receive the PrOD regimen (once-daily dose of 25 mg ombitasvir, 150 mg paritaprevir, 100 mg ritonavir) and dasabuvir (250 mg twice daily) with weight-based RBV for 12 or 24 weeks with additional stratifications based on cirrhosis status, *IL28B* genotype (CC vs non-CC), and HCV treatment history (null/partial vs naive/relapse). Study endpoints included SVR_{12}, as well as measures pertaining to the safety and tolerability of the regimen. Of the 63 patients enrolled, the majority (92%) were male, 67% were treatment naive, 16% had a null response to prior PEG/RBV treatment, 89% were HCV genotype 1a, 19% were at fibrosis stage 4; the mean $CD4^+$ count was >600 cells/μL. Ninety-four percent of patients in the 12-week group achieved SVR_{12}. The SVR rate was 91% for those in the 24-week group receiving the same regimen. There were 2 cases of virologic failure (1 in each arm), both in patients with HCV genotype 1a with cirrhosis and prior null response to pegylated interferon plus RBV. Additionally, 2 cases of HCV reinfection were noted in the 24-week arm. The AEs reported from this study suggested that the PrOD and RBV regimen was well tolerated, as no severe AEs or discontinuations due to AEs occurred. Five patients showed HIV RNA loads ≥40 copies/mL, though none exceeded ≥200 copies/mL during treatment, and all patients resuppressed without a change in their ART regimens. Treatment-emergent AEs were generally mild, the most common being fatigue (48%), insomnia (19%), nausea (18%), and headache (16%). Although study results were derived from a more limited number of patients than other trials, the all-oral, interferon-free, PrOD + RBV regimen also appeared efficacious and well tolerated in those with HIV coinfection [37]. ART regimens were limited in this study; however, additional studies evaluating darunavir- and dolutegravir-treated HIV patients are ongoing. Preliminary results from these studies continue to suggest excellent HCV efficacy with the expected decrease in darunavir trough concentrations without evidence of loss of HIV virologic control [45].

A new DAA regimen combining elbasvir (EBR), an NS5A inhibitor, with grazoprevir (GZR), a second-generation NS3/4A protease inhibitor, was recently approved by the US Food and Drug Administration with an indication for the treatment of chronic HCV genotypes 1 and 4, including in those with HIV-1 coinfection [46]. This regimen was studied in HIV-infected patients in the phase 3, open-label, single-arm C-EDGE CO-INFECTION study. This study investigated the efficacy, safety, and tolerability of EBR/GZR in 218 patients with HIV/HCV coinfection [47]. The treatment regimen was 12 weeks of once-daily oral administration of 50 mg EBR plus 100 mg GZR in a fixed-dose combination tablet. Inclusion criteria were HIV infection, HCV treatment-naive status, and chronic HCV genotype 1, 4, or 6 infection. Patients with cirrhosis were included. Patients had to be either ART naive or stable for at least 8 weeks on 1 of 3 ART regimens: raltegravir, rilpivirine, or dolutegravir with 2 nucleotide/nucleoside reverse transcriptase inhibitors. Those receiving ART had to have CD4 T-cell counts of >200 cells/μL and a screening HIV-1 RNA

concentration <50 copies/mL. For patients not receiving ART, CD4 T-cell counts had to exceed 500 cells/μL. The majority of patients (84%) were male, 17% were African American, 86% were infected with HCV genotype 1 (66% of whom had HCV genotype 1a), and 16% had cirrhosis. Almost all (97%) were taking ART at baseline. Study results demonstrated an SVR_{12} rate of 96%. Importantly, all 35 patients with cirrhosis achieved SVR. Serious AEs were noted in 6 patients, 4 of which occurred after the completion of the dosing phase. None of the serious AEs were judged to be treatment related, and none resulted in patient discontinuation from the study. Two patients on ART had transient HIV viremia during the treatment period. Both patients subsequently achieved undetectable HIV RNA levels with additional compliance education and without a change in their ART regimens. The most frequently observed nonserious AEs were fatigue (13%), headache (12%), and nausea (9%), none of which resulted in study discontinuation. Based on the results of this study, as well as the results of the phase 2 C-WORTHY study which also included HIV-infected subjects, EBR/GZR represents an additional highly efficacious and well-tolerated HCV treatment regimen for HIV-coinfected patients. The data suggest that patients coinfected with HIV responded similarly to HCV-monoinfected patients using standard treatment durations with modern DAA regimens. Drug interactions with ARTs limit the number of HIV regimens that can be combined with EBR/GZR (see companion article in this issue by MacBrayne and Kiser [14]). For most patients, EBR/GZR can be administered as 1 tablet daily without RBV; however, baseline testing for the presence of NS5A resistance-associated variants (RAVs) is recommended in patients with GT 1a infection and guides treatment approaches. The use of RBV and extension to 16 weeks of treatment is recommended for patients with genotype 1a infection and specific baseline NS5A RAVs at any of the key positions (M28A/G/T, Q30 any, L31F/M/V, and Y93 any). These baseline RAVs are found in approximately 5%–10% of the genotype 1a patient population. Patients with genotype 1b and wild-type 1a infection (no RAVs) can be treated for 12 weeks with EBR/GZR alone, including traditionally difficult-to-treat populations such as patients with cirrhosis [48]. Key efficacy outcomes from the aforementioned clinical trials in this section are shown in Table 1. For a full discussion of treatment approaches with this regimen, the reader is directed to updated guidelines on the treatment of HCV infection (www.hcvguidelines.org).

Research into the clinical application of HIV/HCV coinfection treatment strategies continues unabated. Several abstracts describing studies of the real-world performance of DAA regimens were presented at the 2015 annual Conference on Retroviruses and Opportunistic Infections (CROI). One of the studies was an interim report from an ongoing German cohort investigation into the outcomes of patients infected with HCV genotype 1 or 4 treated with SOF-based therapy [49]. Approximately one-third of the 130 patients with available SVR_{12} data were coinfected with HIV. To date, the results of this study have been in alignment with the results of clinical trials and support the concept that HIV coinfection does not adversely impact DAA treatment responses with standard durations of therapy. Specifically, in this cohort treated with SOF-based regimens, the interim SVR_{12} rates were 84% in HCV-monoinfected and 85% in HIV/HCV-coinfected patients. Although the study data did not show an impact of HIV coinfection on responses, cirrhosis was associated with a statistically significant 10% decrease in SVR_{12} rates [49]. An updated presentation from this cohort at the 2016 CROI demonstrated good SVR_{12} rates with 8 weeks of LDV/SOF therapy. The overall SVR_{12} rate was 92% (175/191), including 92% SVR_{12} in 26 HIV/HCV-coinfected patients [50]. While these data are encouraging, the number of HIV/HCV-coinfected patients treated with 8 weeks is small and guidelines currently do not recommend using the 8-week treatment duration in those with HIV (www.hcvguidelines.org).

In an additional study of the combined use of SOF and simeprevir on real-world outcomes, results showed SVR rates of 77% and 71% for the 81 HIV/HCV genotype 1–infected patients and HCV-monoinfected patients, respectively [51]. These SVR rates were very similar (77%–78%) for patients in the study who also had cirrhosis. One-half of the patients who did not achieve SVR_{12} were lost to follow-up and were therefore not considered to be reflective of confirmed virologic failures [51]. Two additional studies examined smaller cohorts of predominantly treatment-experienced HIV/HCV-coinfected patients to determine the efficacy of the combined SOF and simeprevir regimen. These 2 studies showed SVR rates of 93%–95% at 12 weeks [52, 53]. The results of these smaller studies are also consistent with results found in a clinical trial (92%–94%) [54]. In all of these real-world evaluations, treatment of HCV using SOF-based regimens was generally well tolerated, with the exception of the expected anemia associated with the addition of RBV.

Although not as prevalent in the United States as genotype 1, genotypes 2 and 3 make up a significant proportion of HCV infections worldwide [55]. While treatment approaches for these genotypes continue to evolve, SOF plus RBV remains the treatment of choice for genotype 2 infection. Two phase 3 clinical trials (PHOTON-1 and PHOTON-2) investigated the safety and efficacy of SOF/RBV for the treatment of HCV in patients coinfected with HIV-1 [56, 57]. In PHOTON-1, an open-label, nonrandomized, uncontrolled trial of 223 HCV/HIV-coinfected individuals conducted for this purpose, inclusion criteria consisted of infection with HCV genotypes 1, 2, or 3, as well as HIV RNA levels of ≤50 copies/mL and a CD4 count >200 cells/μL in those receiving treatment with the majority of existing ART regimens [56]. Those with untreated HIV infection and a CD4 count >500 cells/μL were also eligible. For the 41 non-treatment-naive patients who had been treated with PEG/RBV, all had HCV genotypes 2 or 3. Treatment-naive

patients with HCV genotypes 2 or 3 were administered 400 mg of SOF and weight-based RBV for 12 weeks. All others (treatment-naive patients with HCV genotype 1, treatment-experienced patients with HCV genotype 2 or 3) received the same regimen for 24 weeks. It is important to note that the addition of more efficacious therapies for genotypes 1 and 3 has resulted in the removal of SOF/RBV as a recommended treatment for persons with these genotypes (www.hcvguidelines.org).

Treatment-experienced patients had higher rates of cirrhosis, the median CD4 cell count among all patients was between 562 and 581 cells/μL, and 90%–98% of patients in each of the 3 treatment groups were on ART. The majority (79%) of treatment-naive patients with HCV genotype 1 carried the 1a subtype, and 32% of those patients were African American. SVR_{12} was achieved in 76% of HCV genotype 1–infected patients, 88% in genotype 2 patients, and 67% in genotype 3 patients. The majority of treatment-experienced patients with HCV genotypes 2 (92%) or 3 (94%) achieved SVR_{12}. In both the 12- and 24-week regimens, the discontinuation rates were low at 3% and 4%, respectively. No serious AEs considered to be related to the study drugs were observed, and the most common AEs included fatigue, insomnia, nausea, and headache. All AEs were considered to be mild to moderate in severity (grade 1 or 2). Laboratory abnormalities including decreases in hemoglobin and absolute CD4 T-cell counts were detected, although these were expected as known effects of RBV therapy. Importantly, no AEs pertaining to HIV disease or its treatment were detected [56].

Based on the PHOTON-1 trial, the PHOTON-2 trial was designed to explore the effects of the same treatment regimen using the same inclusion criteria in patients with HCV genotype 4, as well as to replicate benefits observed following longer treatment durations for patients with HCV genotype 3, as opposed to those with genotype 2, regardless of HCV treatment history [57]. Although the medications in the regimen were unchanged, the duration of administration differed. Patients received 24 weeks of treatment, with the exception of treatment-naive patients with HCV genotype 2, who received a 12-week regimen. Two hundred seventy-four patients were included in the final analysis, 19 of whom were treatment naive with HCV genotype 2, 55 treatment-experienced persons with HCV genotype 2 or 3, and 200 treatment-naive persons with HCV genotype 1, 2, 3, or 4. The majority of patients (80%) were HCV treatment naive. Of the treatment-experienced patients, the majority (89%) were HCV genotype 3. One-fifth of the patients (20%) had cirrhosis, although a higher prevalence was noted in treatment-experienced patients. ART was very common, as demonstrated by treatment rates of 89%–100% across all of the treatment groups [57]. SVR_{12} was 85% in patients with HCV genotype 1, 88% in patients with HCV genotype 2, 89% in patients with HCV genotype 3, and 84% in patients with HCV genotype 4. The SVR_{12} rates for treatment-naive patients with HCV genotype 2 or 3 (89% and 91%, respectively) were relatively close to those observed in treatment-experienced patients (83% for HCV genotype 2 and 86% for HCV genotype 3, respectively). The SVR_{12} rate for treatment-naive HCV genotype 1 patients with cirrhosis (65%) was substantially lower than that observed in HCV genotype 3 patients with cirrhosis (78%). Only1% of the study patients experienced treatment-related serious AEs (2 had anemia, 1 developed thrombocytopenia and petechiae, and 1 had mania). The serious AEs experienced by these 4 patients all resolved by the end of the follow-up period. A small number of patients (2%), all of whom were included in the 24-week regimen, discontinued due to an AE. The incidence of AEs was similar between the groups, the most common being fatigue, insomnia, asthenia, and headache. Most of these AEs were considered to be mild or moderate in severity. Study results also indicated that 1% of the patients receiving ART experienced a transient HIV viral replication, although none required changes in their ART regimens. The most common laboratory abnormalities detected were decreased hemoglobin concentrations and increased total bilirubin. Collectively, the results from PHOTON-1 and -2 demonstrated comparable efficacy and safety results with SOF/RBV in persons with HIV/HCV coinfection. Currently SOF/RBV is only indicated for those infected with genotype 2 HCV, including those with HIV coinfection.

Comprehensive HIV/HCV coinfection management recommendations have been put forth by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (www.hcvguidelines.org). These recommendations include specific management strategies targeted to all HCV genotypes and disease stages including treatment-experienced and cirrhotic patients. A dedicated coinfection section contains additional information on the relevant HCV studies in this population and unique treatment considerations relating to drug–drug interactions [14].

REINFECTION FOLLOWING HCV TREATMENT

While the high rates of HCV cure in persons with HIV coinfection are encouraging, HCV reinfection following HCV cure is a concern that deserves more attention. Persons infected with HIV who engage in high-risk behaviors following treatment appear especially prone to reinfection. This concern was highlighted by the findings of a recent meta-analysis of 66 studies and >11 000 participants presented at CROI 2015. The results of the meta-analysis, which was focused on late recurrence (late relapse or reinfection) of HCV after achievement of SVR_{12}, revealed that the risk of HCV reinfection was variable and largely based on the patient's risk category (high vs low) and HIV serostatus [58]. The high-risk categories included HIV-uninfected injection drug users and those who were incarcerated. The low-risk category included all other HCV-monoinfected persons. Those with HIV/HCV coinfection showed the highest 5-year rate of HCV infection recurrence (21.7%). The lowest

level of 5-year reinfection with HCV was seen in those with a low-risk profile (1.14%), whereas the reinfection rate was 13.2% in persons in the HCV-monoinfected high-risk group. The study authors posited that large differences in event rates according to risk grouping made reinfection significantly more likely than late relapse [58]. It should be noted that many of the studies of HIV/HCV-coinfected patients included men who have sex with men (MSM) acutely infected with HCV that was presumed to be sexually transmitted [34, 59]. Caution should be taken not to extrapolate these reinfection rates to a general HIV/HCV-coinfected population.

Additional cases of HCV reinfection in those with HIV were detected in an analysis of 2 patients in the TURQUOISE-I trial conducted by Sulkowski et al [37]. In that study, HCV reinfection occurred in 2 patients who had achieved SVR_{12} after a 24-week course of treatment. Through phylogenetic sequence analysis, these patients had convincing evidence of reinfection with a unique strain of HCV genotype 1a compared to the pretreatment virus. Based on patient self-reports, both had engaged in high-risk (sexual) behaviors for HCV infection [37]. Previous studies have produced similar findings, indicating that reinfection rates are higher in HIV-infected individuals with high-risk behavior [34]. A recently updated report from the C-EDGE CO-INFECTION study also demonstrated 2 likely HCV reinfections by the SVR_{24} follow-up time point [35]. Based on accumulating data, HIV-infected MSM, particularly those presenting and treated during acute HCV infection, appear to be at high risk for reinfection within a relatively short period of time. Collectively, these data suggest that a renewed emphasis on harm reduction and safe sex practices counseling, combined with a clear message from providers that HCV reinfection can occur, is needed for HIV-infected MSM. The HCV care continuum does not end with HCV cure in persons at risk for reinfection and must incorporate ongoing harm reduction efforts. Widespread, effective HCV treatment in this population to reduce the risk of reinfection (ie, HCV treatment as prevention) is an intriguing area that requires further study.

CONCLUSIONS

Due to the potential for rapid progression, HCV treatment should be a high priority in persons with HIV coinfection even in the absence of advanced fibrosis. HCV treatment efficacy is no longer a major consideration in the treatment of persons with HIV as this group of patients can achieve HCV cure at the same rate in persons without HIV, with some possible exceptions when shorter durations of treatment are used such as 8 weeks of therapy. Importantly, recent studies have convincingly shown that SVR_{12} rates achieved with new oral HCV regimens are high in both clinical trials and real-world settings. To achieve optimal patient outcomes, HCV treatment is best delivered to HIV-coinfected patients using a multidisciplinary approach including pharmacists, HIV treatment experts, and liver disease specialists. It is incumbent on practitioners to carefully review a patient's HIV treatment history before switching therapies to accommodate HCV treatment. Last, practitioners should understand the risks for HCV reinfection and inform patients of measures they can take to protect themselves and others.

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